17th Street NW., Room 501, Washington, DC 20506.

All submissions must be in English and should conform to the information requirements of 15 CFR 2007.

A party must provide ten copies of its submission which must be received at USTR no later than noon on November 1, 1994. If the submission contains business confidential information, ten copies of a non-confidential version must also be submitted. A justification as to why the information contained in the submission should be treated confidentially must be included in the submission. In addition, any submissions containing business confidential information must be clearly marked "confidential" at the top and bottom of the cover page (or letter) and of each succeeding page of the submission. The version that does not contain confidential information should also be clearly marked, at the top and bottom of each page, "public version" or "non-confidential."

Written comments submitted in connection with this request, except for information granted "business confidential" status pursuant to 15 CFR 2007.7, will be available for public inspection shortly after the filing deadline. Inspection is by appointment only with the staff of the USTR Public Reading Room and can be arranged by calling (202) 295–6186.

Frederick L. Montgomery,

Chairman, Trade Policy Staff Committee.

[FR Doc. 94–24363 Filed 9–30–94; 8:45 am]

BILLING CODE 3190–01–M

Sunshine Act Meetings

Federal Register
Vol. 59, No. 190
Monday, October 3, 1994

This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

COMMODITY CREDIT CORPORATION

TIME AND DATE: 2:00 p.m., October 11, 1994.

PLACE: Room 104–A Administration Building, U.S. Department of Agriculture, Washington, D.C.

STATUS: Open.

MATTERS TO BE CONSIDERED:

1. Special Open Meeting of March 22, 1994.
2. Memorandum re: Update of Commodity Credit Corporation (CCC)-Owned Inventory.
3. Memorandum re: Commodity Credit Corporation's (CCC,s) Financial Condition Report.
4. Memorandum re: Commodity Credit Corporation's (CCC's) Annual Financial Statement and Related Activities.
5. Docket CZ–161a, Revision 6 re: Policies for Collection, Settlement, and Adjustment of Certain Claims By or Against the Commodity Credit Corporation.
6. Memorandum re: Revised Availability of Commodity Credit Corporation Stocks for Donation Overseas Under Section 416(b) of the Agricultural Act of 1949, as Amended, for Fiscal Year 1994.
7. Memorandum re: Availability of Commodity Credit Corporation Stocks for Donation Overseas Under Section 416(b) of the Agricultural Act of 1949, as Amended, for Fiscal Year 1995.
8. Resolution re: Docket CZ–266, Resolution No. 32, Ratification of Commodities Available for Public Law 480 During Fiscal Year 1995.

CONTACT PERSON FOR MORE INFORMATION: Deborah A. Dawson, Secretary, Commodity Credit Corporation, Room 3603 South Building, U.S. Department of Agriculture, Post Office Box 2415, Washington, DC 20013; telephone (202) 690–0490.

Dated: September 29, 1994.

Deborah A. Dawson,

Secretary, Commodity Credit Corporation.

[FR Doc. 94–24545 Filed 9–29–94; 3:23 pm]

BILLING CODE 3410–05–M

U.S. CONSUMER PRODUCT SAFETY COMMISSION

TIME AND DATE: 10:00 a.m., Wednesday, October 5, 1994.

LOCATION: Room 420, East West Towers, 4330 East West Highway, Bethesda, Maryland.

STATUS: Open to the Public.

MATTER TO BE CONSIDERED:

Voluntary Standards/International Activities

The staff will brief the Commission on voluntary standards and international activities.

For a recorded message containing the latest agenda information, call (301) 504–0709.

CONTACT PERSON FOR ADDITIONAL INFORMATION: Sadye E. Dunn, Office of the Secretary, 4330 East West Highway, Bethesda, MD 20207 (301) 504–0800.

Dated: September 29, 1994.

Sadye E. Dunn,

Secretary.

[FR Doc. 94–24544 Filed 9–29–94; 3:18 pm]

BILLING CODE 6355–01–M

FEDERAL ENERGY REGULATORY COMMISSION

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT: September 26, 1994, 59 FR 49103.

PREVIOUSLY ANNOUNCED TIME AND DATE OF MEETING: September 28, 1994, 10:00 a.m.

CHANGE IN THE MEETING: The following Docket Numbers have been added on the Agenda scheduled for September 28, 1994:

Item No., Docket No., and Company

CAG–10 RP94–67–000, *et al.*, Southern Natural Gas Company
CAG–12 RP94–150–000, *et al.*, ANR Pipeline Company
CAG–34 TM94–4–32–000 and 001, Colorado Interstate Gas Company

Lois D. Cashell,

Secretary.

[FR Doc. 94–24426 Filed 9–28–94; 4:47 pm]

BILLING CODE 6717–01–M

federal register

Monday
October 3, 1994

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 314
Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 314

[Docket No. 85N–0214]

RIN 0905–AB63

Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing regulations on certain requirements governing the submission, review, and approval of abbreviated new drug applications (ANDA's). Specifically, these new regulations pertain to patent issues, certification and notice of certification of invalidity or noninfringement of a patent by ANDA applicants, effective date of approval of an application under the Federal Food, Drug, and Cosmetic Act (the act), and new drug product exclusivity. These regulations are intended to complete FDA's implementation of Title I of the Drug Price Competition and Patent Term Restoration Act of 1984.

EFFECTIVE DATE: November 2, 1994.

FOR FURTHER INFORMATION CONTACT: Sharon M. Sheehan, Center for Drug Evaluation and Research (HFD–600), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–0340.

SUPPLEMENTARY INFORMATION:

I. Background

On September 24, 1984, the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (the 1984 amendments) was enacted. The law consisted of two different titles. Title I authorized the approval of duplicate versions of approved drug products (other than those reviewed and approved under section 507 of the act (21 U.S.C. 357)) under an ANDA procedure. Title II authorized the extension of patent terms for approved new drug products (including antibiotics and biological drug products), some medical devices, food additives, and color additives. Congress intended these provisions to provide a careful balance between promoting competition among brand-name and duplicate or "generic" drugs and encouraging research and innovation.

Title I also amended section 505 of the act (21 U.S.C. 355) by requiring all New Drug Application (NDA) applicants and holders to provide certain patent information, requiring ANDA applicants to certify as to the status of patents claiming the drug product they intend to copy, providing for the submission and approval of applications for which the investigations relied on by the applicant to satisfy the "full reports" of safety and effectiveness requirements were not conducted by the applicant or for which the applicant had not obtained a right of reference or use from the person who conducted the investigations, establishing rules for disclosure of safety and effectiveness data submitted as part of an NDA, and providing specific time periods during which an NDA or an ANDA cannot be submitted or approved. The 1984 amendments also required FDA to promulgate new regulations implementing the statute. In the **Federal Register** of July 10, 1989 (54 FR 28872), FDA published a proposed rule on Title I. In the **Federal Register** of April 28, 1992 (57 FR 17950), FDA published a final rule on some aspects of Title I, such as ANDA content and format, approval and nonapproval of an application, and suitability petitions. In that final rule, FDA stated that it was still examining issues concerning patents and market exclusivity, and would issue a final rule once it had completed its deliberations. This document now finalizes those provisions.

In the **Federal Register** of March 7, 1988 (53 FR 7298), FDA published a final rule implementing Title II. That rule is codified at 21 CFR part 60.

II. Highlights of the Final Rule

A. Patent Information, Certification, and Notice of Certification to Patent Owner and Certain Application Holders

The statute prohibits the agency from making effective the approval of an ANDA or an application described by section 505(b)(2) of the act (referred to as a 505(b)(2) application) before all relevant product and use patents for the listed drug (a drug product listed in an approved drug product list published by the agency) have expired, except where the generic applicant asserts either that its product will not infringe the patent or that the patent is invalid. In the latter case, approval of the ANDA or the 505(b)(2) application may not be made effective until the patent owner and the NDA holder have been notified and have had an opportunity to litigate the issue of patent infringement or validity. To facilitate the patent protection provisions, the statute requires that applications submitted under section 505(b) of the act include the patent number and expiration date of all relevant patents that claim the drug (including product and formulation patents) in the application or use patents that claim a method of using the drug. The agency publishes this patent information in its approved drug product list ("Approved Drug Products With Therapeutic Equivalence Evaluations," also known as the "Orange Book") for each listed drug for which patent information has been submitted.

A generic drug applicant submitting an ANDA that refers to a listed drug must include a certification as to the status of all patents applicable to the listed drug. Similarly, an applicant submitting a 505(b)(2) application must make certifications with respect to patents claiming any listed drug or claiming a use for such listed drug. If a generic applicant certifies that a relevant patent expires on a specified date, the effective date of approval of the ANDA or 505(b)(2) application will be delayed until the expiration of the patent. Thus, for example, if the patent expired on January 1, 1995, the effective date of approval of the ANDA or 505(b)(2) application would be January 1, 1995. The agency regards drug products with delayed effective dates as having tentative approvals; it does not consider the approval to be final until the effective date and the issuance of a final approval letter (see 57 FR 17950 at 17956). When a generic applicant certifies that any product or use patent is invalid or will not be infringed, the applicant must give notice of such certification to the patent owner and appropriate approved application holder for the listed drug. The generic applicant must include in the notice the factual and legal basis for the applicant's opinion that the patent is invalid or will not be infringed. Finally, a patent owner has 45 days from receipt of the notice of certification to file suit against the generic applicant to defend the patent. If the patent owner files suit within 45 days, the effective date of approval of the ANDA or 505(b)(2) application may be delayed up to 30 months pending resolution of the lawsuit.

The final rule describes: (1) The requirements for the submission of patent information by an NDA holder or applicant, (2) the patent certification requirements applicable to generic applicants, and (3) the content of a patent certification notice. The final rule also specifies: (1) When and to whom the notice is to be sent, and (2) the effect of each type of patent certification on

the effective date of approval of an application for a generic drug product.

B. Exclusivity

Section 505(c)(3)(D) and (j)(4)(D) of the act protects certain listed drugs, or certain changes in listed drugs, from generic copying for specified periods by placing a moratorium on the submission, or by delaying the effective date of approval, of ANDA's and 505(b)(2) applications for those listed drugs. These so-called "exclusivity provisions" provide the following periods of protection from generic competition: (1) A 10-year period of exclusivity for new chemical entities approved during the period January 1, 1982, to September 24, 1984, the date of enactment of the 1984 amendments; (2) a 5-year period of exclusivity for new chemical entities approved after September 24, 1984; (3) a 3-year period of exclusivity for drugs that are not new chemical entities approved after September 24, 1984, if the applicant submitted an application containing reports of "new clinical investigations (other than bioavailability studies) essential to approval and conducted or sponsored by the applicant"; (4) a 3-year period of exclusivity for certain changes made after September 24, 1984, if the applicant submitted a supplement containing reports of "new clinical investigations (other than bioavailability studies) essential to approval and conducted or sponsored by the person submitting the application"; and (5) a 2-year period of exclusivity for drugs that are not new chemical entities, or for certain changes made to already approved drug products, approved during the period January 1, 1982, to September 24, 1984.

The agency is codifying the provisions regarding 5- and 3-year exclusivity; FDA is not codifying the other exclusivity provision because they have expired. The final rule also defines certain terms used in the regulations, and clarifies the agency's interpretation of each of the provisions.

III. Comments on the Proposed Rule

A. Section 314.50—Content and Format of an Application (21 CFR 314.50)

The proposed rule contained several additions to the existing requirements in § 314.50. The proposed additions focused on patent information and certifications and claimed exclusivity. Under proposed § 314.50(i), for example, a 505(b)(2) applicant would be required to include in its application one of four possible certifications: (1) That patent information on the reference listed drug had not been submitted to FDA; (2) that the patent had expired; (3) the date on which the patent will expire; or (4) that the patent was invalid or would not be infringed by the manufacture, use, or sale of the proposed drug product.

1. Two comments objected to the provision regarding use patents (patents that claim a use for the patented invention) under proposed § 314.50(i). The comments explained that the provision would permit applicants to decide whether a use would infringe a patent and whether the patent owner should be notified. Both comments asked FDA to require applicants to send a certification of invalidity or noninfringement to all patent owners whose patents claim the active ingredient involved in the proposed drug product. One comment would also revise the provision to withhold approval of an application if the patent owner disagreed with the patent certification in order to give the patent owner an opportunity to initiate a lawsuit.

The regulation corresponds to the statutory language at section 505(b)(2)(B) of the act. The statute does not require a patent certification with respect to a use patent if the applicant is seeking approval for a drug product that does not claim a use protected by the patent. FDA also declines to revise the provision to have FDA withhold approval of an application under these circumstances. The statute provides express and specific grounds for delaying an effective date of approval (see section 505(c)(3) of the act). These do not include any express authority to delay an effective date of approval based on an inadequate notice, and the agency is not prepared to infer such authority. NDA holders are advised, however, to notify FDA of the patented uses that appear in the approved labeling for their products; this will enable the agency to provide some guidance to applicants required to submit either a patent certification under section 505(b)(2)(A) or (j)(2)(A) of the act, or a statement under section 505(b)(2)(B) or (j)(2)(A)(viii) of the act. These uses will be listed in the Orange Book.

2. One comment noted that "United States Office of Patent and Trademark" in proposed § 314.50(i)(1)(i) should be "United States Patent and Trademark Office."

FDA agrees and has revised the provision accordingly.

3. One comment asked FDA to give examples of patent certifications under proposed § 314.50(i)(1)(i)(A)(*1*) to (i)(1)(i)(A)(*3*). As proposed, these provisions would require an applicant to certify that: (1) No patent information had been submitted to FDA, (2) the patent has expired, or (3) the patent would expire on a specific date.

Generally, most applicants making paragraph I, II, or III patent certifications simply paraphrase the language used in § 314.50(i)(1)(i)(A)(*1*) to (i)(1)(i)(A)(*3*) for each patent.

4. The agency, on its own initiative, has amended § 314.50(i)(1)(i)(A) to replace the reference to a patent that claims "the drug or drugs" with a patent that claims "a drug (the drug product or drug substance that is a component of the drug product)." The agency has made this amendment to clarify the types of patents for which a certification should be made.

5. The agency, on its own initiative, has also amended § 314.50(i)(1)(i)(A)(*4*) and § 314.94(a)(12)(i)(A)(*4*) (21 CFR 314.94(a)(12)(i)(A)(*4*)) to include a reference to unenforceable patents. As proposed, these provisions would have required applicants to certify that a patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product that is the subject of the application. The agency has revised these certification statements to clarify how an applicant challenging a patent as unenforceable should word its paragraph IV certification. Although the agency realizes that courts have, in patent cases, distinguished invalid patents from unenforceable patents, the only court addressing the issue of unenforceable patents in the context of the provisions of section 505 of the act interpreted the phrase "invalid or not infringed" to include an unenforceable patent. (See *Merck* v. *Danbury Pharmacal, Inc.*, 694 F.Supp. 1 (D. Del. 1988), *aff'd*, 873 F.2d 1418 (Fed. Cir. 1989) (applying section 505(j)(4)(B)(iii) of the act).) The agency agrees with the court's construction of the act. The alternative interpretation, precluding applicants challenging patents as unenforceable from filing certifications under paragraph IV, would be contrary to Congress' obvious intent in allowing patent challenges under section 505 of the act and would lead to absurd results. Subsequent to the *Merck* decision, the agency has accepted paragraph IV certifications from applicants challenging patents as unenforceable.

The agency has also made corresponding changes to other provisions, such as the notice requirements in §§ 314.52 and 314.95, to include certifications for "unenforceable" patents.

6. Two comments disagreed with proposed § 314.50(i)(1)(ii), which would require an applicant to state that, in its opinion and to the best of its knowledge, there are no patents that

claim the drug or drugs on which investigations that the applicant relied upon in its application were conducted or that claim a use for the drug or drugs. One comment said applicants should only be required to certify that there are no listed patents. The other comment suggested deleting the provision and combining this patent certification with a paragraph I (no patent information submitted) certification.

FDA believes the comments have misconstrued proposed § 314.50(i)(1)(ii). The provision would require a "no relevant patents" certification if, "in the opinion of the applicant and to the best of its knowledge," there are no patents described in the patent certification section (§ 314.50(i)(1)(i)). In other words, if an applicant made one of the four patent certifications under § 314.50(i)(1)(i), the applicant would not make another certification under § 314.50(i)(1)(ii).

7. One comment strongly objected to proposed § 314.50(i)(4). The provision would require section 505(b)(2) applicants whose applications were submitted after the late patent information is filed, or did not contain an appropriate patent certification at the time of the late submission, to submit a patent certification on such patents. The comment explained that section 505(d)(6) and 505(e)(4) of the act authorizes the agency, after providing an opportunity for a hearing, to refuse to approve an application or to withdraw approval of an NDA for failure to provide patent information. Thus, the comment argued that proposed § 314.50(i)(4) conferred a benefit on NDA applicants by permitting late patent information submissions without applying the statutory requirements for timely submission.

The agency has considered this and other comments which suggest regulatory approaches for handling patents that are filed outside the statutory time limits. Congress clearly intended to enforce timely submission of patent information. The statute requires that patent information be submitted with the application, by amendment prior to approval of the application, or within 30 days after the patent issues. (See 21 U.S.C. 355(b)(1) and (c)(2)). For the most extreme example of untimely patent filing—when a pioneer fails to file required patent information within 30 days of notice from the agency—Congress has provided the extreme remedy of withdrawal of approval of the new drug application. (See 21 U.S.C. 355(e)(4)). Congress did not directly address the question of patent filings that occur more than 30 days after issuance of the patent and for which the agency does not provide notice of the deficiency. The agency could treat these filings in a number of ways. The agency could refuse to publish in the list the untimely patent information. This approach has been rejected because it would provide no notice to subsequent 505(b)(2) or ANDA applicants that a patent exists that the NDA holder believes is applicable to the pioneer drug product. Absence of publication could lead an applicant to submit a 505(b)(2) application or an ANDA that it would not have submitted had the patent been listed. As a result, the applicant and the agency may expend resources unnecessarily. In addition, 505(b)(2) or ANDA applicants could thereby subject themselves and the NDA holder to unnecessary patent litigation.

Prior to publication of the proposed rule, the agency was asked to consider regulatory language designed to allow a pioneer holder to update, at any time, its patent information. This approach has been rejected because it would allow for manipulation of the patent filing system by the holder of the NDA and could result in delays in approval of otherwise approvable ANDA's. For example, if patents could be filed at any time after issuance, the holder of the NDA could delay the filing of a patent, and subsequent publication, until within 30 months prior to the expiration of the latest-expiring patent. Even if the ANDA applicant does not believe the patent is applicable to the pioneer drug, it will then be required either to file a paragraph III certification and wait until the patent expires, or to file a paragraph IV certification and therefore initiate the procedure set out at section 505(c)(3)(C) and (j)(4)(B). This procedure requires that the agency wait at least 30 months, unless a shorter or longer period is judicially ordered, before it makes effective approval of the application. Even if the NDA holder is unsuccessful in defending the late-filed patent, it will have extended its period of market monopoly in a manner inconsistent with the intent of Congress when it struck the balance between protecting the patent rights of innovators and encouraging prompt and efficient entry of generics onto the market. By requiring timely filing of patent information, the agency hopes to permit judicial resolution of patent disputes without unduly extending the innovator's period of patent protection.

The approach adopted by the agency as best embodying the compromise adopted by Congress requires that if an NDA applicant submits required patent information on an approved drug product more than 30 days after issuance of the patent, FDA will publish the untimely information, but will not require ANDA and 505(b)(2) applicants with pending applications who have previously submitted a certification, i.e. those applicants who would be prejudiced by the late submission, to recertify to the new patent. Only applicants who initially submit ANDA's or 505(b)(2) applications after the submission of the patent information or whose pending applications do not contain a valid certification at the time of submission would be required to submit a certification as to that patent. (See §§ 314.50(i)(4) and 314.94(a)(12)(vi).) While this could result in two categories of ANDA's for a pioneer drug, those without certifications for the late-filed patent and those with certifications for that patent, this approach is the best means for discouraging manipulation of the patent filing scheme and providing optimum notice of applicable patents. Disputes over patent issues arising from this approach will be resolved by Federal courts.

It is the agency's opinion that this remedy may also prove suitable in certain instances when an NDA holder fails to respond to an agency request for patent information within the statutory 30-day period. It is a less severe sanction than withdrawing the approval of the NDA, but nonetheless effectuates congressional intent to encourage timely filing and protect patent rights.

8. One comment asked FDA to clarify supplemental patent certifications under proposed § 314.50(i)(6)(i). The comment noted that the provision would have applicants submit new patent certifications if a patent were found valid and infringed, but does not instruct applicants what to do if a patent is found to be infringed, but also invalid.

FDA has revised §§ 314.50(i)(6)(i) and 314.94(a)(12)(vii)(A) to state that an applicant does not have to provide an amended patent certification if a court finds a patent to be invalid and infringed. FDA recognizes that courts have the discretion to focus on patent infringement issues and not decide patent validity. However, court decisions have also recognized the desirability of a court ruling on patent infringement even if the patent is held invalid. (See, e.g., *Medtronic, Inc.* v. *Cardiac Pacemakers, Inc.*, 721 F.2d 1563 at 1583 (Fed. Cir. 1983).) ("Though an invalid claim cannot give rise to liability for infringement, whether it is infringed is an entirely separate question capable of determination without regard to its validity. Because

both validity and infringement involve construction of a claim, and because the construction must be the same in determining both, it is desirable to decide both questions at the same time.") Moreover, in such instances, the Supreme Court has indicated that "of the two questions, validity has the greater public importance." (See *Sinclair & Carroll Co.* v. *Interchemical Corp.*, 325 U.S. 327, 330 (1945).) Consequently, if a court finds a patent to be invalid and infringed, FDA will attach more importance to the finding of invalidity, and will not require an amended patent certification even if the patent is also found to be infringed.

9. The agency, on its own initiative, has also revised § 314.50(i)(6)(ii) regarding patent certifications when a patent is removed from the list of patents for any reason other than a declaration of invalidity. Section 314.50(i)(6)(ii), as proposed, would have required an applicant to certify that there are no patents that claim the drug or, if other relevant patents claim the drug, to submit a request to withdraw the paragraph IV (patent is invalid, unenforceable, or will not be infringed) certification. FDA has revised this section so that an applicant must certify that there are no patents that claim the drug or, if other relevant patents claim the drug, to provide an appropriate patent certification.

10. On its own initiative, the agency has also revised § 314.50(i)(6)(iii)(*b*) (now renumbered as § 314.50(i)(6)(iii)(B)). As proposed, this provision would not require an applicant to amend a patent certification "when information on an otherwise applicable patent is submitted after the 505(b)(2) application is approved, whether or not the approval of the abbreviated application is effective." Because an approval with a delayed effective date is tentative and is not final (see 57 FR 17950 at 17956), the agency has revised § 314.50(i)(6)(iii)(B) to require section 505(b)(2) applicants to amend their patent certifications until the effective date of approval.

11. FDA received five comments on proposed § 314.50(j) and the applicant's obligations when claiming marketing exclusivity for a product. One comment would change proposed § 314.50(j) to have an applicant submit exclusivity information "with" its application rather than "to" its application.

FDA agrees, in part, with the comment. In general, applicants should submit exclusivity information with their NDA's. If the NDA has been submitted, but has not been approved, the applicant should submit exclusivity information as an amendment.

12. One comment would revise proposed § 314.50(j)(3) to have an applicant state that, "to the best of its knowledge or belief, a drug has not been approved." The comment said proposed § 314.50(j)(3) would require applicants to "prove a negative" because they would have to show that "no drug has previously been approved under section 505(b) of the act containing any active moiety in the drug for which the applicant is seeking approval."

FDA agrees and has amended the rule accordingly.

13. Proposed § 314.50(j)(4)(i) contained a typographical error. As originally drafted, the provision interpreted "new clinical investigations" as a certification that, to the best of the applicant's knowledge, the clinical investigations included in the application "meet the definitions of 'new' and 'clinical investigations' set forth in § 314.108(a)." Proposed section 314.108(a), however, only defined "new clinical investigation." The agency has corrected § 314.50(j)(4)(i) to refer to "new clinical investigation." The agency has also replaced the reference to "the clinical investigations" with "each of the clinical investigations." This change is intended to clarify that each clinical investigation, as opposed to some clinical investigations, must meet the definition of a "new clinical investigation" in § 314.108. The agency has also made a minor grammatical change to § 314.50(j)(4) to simplify its sentence structure.

14. Proposed § 314.50(j)(4)(ii) interpreted the phrase "essential to approval" as:

> A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval, a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the application, and an explanation as to why the studies or reports are insufficient.

Three comments would revise proposed § 314.50(j)(4)(ii) to have FDA declare whether a study is "essential to approval" before the applicant begins the study or at the applicant's request. Another comment would consider the agency's rejection of a suitability petition or ANDA as conclusive evidence that studies are "essential to approval."

As stated elsewhere in this final rule, determining whether a study is essential for approval before a firm submits an application or even begins the study is not always feasible. Research goals and objectives often change during clinical investigations. Moreover, as stated in the preamble to the proposed rule, one cannot determine what studies will be essential to approval of an application by a review of protocols without knowing what drugs have been approved and what is in the published literature at the time the application is approved. If published reports of investigations, other than those conducted or sponsored by the applicant, are sufficient to approve a drug product, no additional studies would be essential to approval of that drug product as of the date of approval, and no exclusivity would be granted (see 54 FR 28872 at 28900 and 28901). Thus, it is far more practical for FDA to decide whether a study is essential for approval at the time the application is approved. FDA also believes that, if a pivotal study that could form the basis for approval were published by someone other than the applicant after submission but before approval of the application, there would be no exclusivity.

The agency also declines to treat its rejection of a suitability petition or ANDA as conclusive evidence that studies are "essential to approval." FDA may refuse to approve a suitability petition or ANDA for a variety of reasons. For example, under 21 CFR 314.93(e)(1)(ii), the agency may not approve a suitability petition that seeks to change an active ingredient if the drug product that is the subject of the petition is not a combination drug. Under 21 CFR 314.127(a), the agency may refuse to approve an ANDA if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are inadequate to ensure and preserve its identity, strength, quality, and purity. Thus, the agency's refusal to approve a suitability petition or ANDA does not necessarily mean that studies conducted or sponsored by the applicant are "essential to approval."

15. One comment also interpreted the terms "scientific literature" in proposed § 314.50(j)(4)(ii) as literature existing at the time the application was submitted.

FDA agrees that § 314.50(j)(4)(ii) only requires applicants to provide a list of all published studies or publicly available reports of clinical investigations known to the applicant at the time the applicant submits the application.

B. Section 314.52—Notice of Certification of Invalidity or Noninfringement of a Patent

Proposed § 314.52 described the process whereby an applicant would provide notice of certification of invalidity or noninfringement of a patent. Proposed § 314.52(a) would have required applicants to provide notice to each patent owner that is the subject of the certification and the holder of the approved application. Proposed § 314.52(b) instructed applicants to provide notice after receipt of a letter from FDA stating that the application has been filed. Proposed § 314.52(c)(6) specified the content of a notice, including a "detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." Proposed § 314.52(d) would have required an applicant who amended its application to contain a patent certification to provide notice of certification of invalidity or noninfringement of a patent. Proposed § 314.52(e) would have required applicants to document receipt of notice.

16. FDA received two comments on proposed § 314.52(a). One comment agreed with the provision, but stated that notice to the holder of the approved application should be considered only as informational "with no legal ramifications since the NDA holder has *no* patent rights by reason of its NDA." (Emphasis added in original.)

The legal ramifications under patent law, if any, of this notice of certification of invalidity or noninfringement of a patent are beyond the scope of this rulemaking.

17. One comment objected to proposed § 314.52(a)(3). The comment explained that the provision would permit an applicant whose application did not cover any use claimed in a patent to refrain from making any patent certifications or providing any notice. The comment would require all applicants to provide notice of certification of invalidity or noninfringement of a patent to all patent owners whose patents claim the active ingredient that is the subject of the application.

Under section 505(b)(2)(A) of the Act, an application must contain a certification with respect to each patent which claims the listed drug or which claims a use for such listed drug for which the 505(b)(2) applicant is seeking approval. One of these patent certifications is that the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted. (See section 505(b)(2)(A)(iv) of the Act). If an applicant makes a "paragraph IV" certification, it must give notice to the patent owner and the NDA holder. (See section 505(b)(3)(A) of the Act.) If, however, the applicant is not seeking approval for a use that is covered by a use patent, the statute does not require a "paragraph IV" certification or notice to that patent owner and NDA holder. (See section 505(b)(2)(B) and (b)(2)(A) of the Act.)

Thus, § 314.52(a) is consistent with the statute, and FDA declines to revise it as suggested by the comment.

18. FDA received three comments on proposed § 314.52(c) regarding the content of a notice of certification of invalidity or noninfringement of a patent. Two comments favored extremely detailed statements of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed. These comments would require the applicant to list all components used in the proposed drug product, the proportions of each component, and list all grounds supporting its opinion that the patent is invalid or will not be infringed. One comment opposed disclosure of the proposed drug product's formulation and also objected to the use of a "designated intermediary" in proposed § 314.52(c)(6)(iii).

In general, the statute requires a notice of certification of invalidity or noninfringement of a patent to state that an application has been submitted and to include "a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." (See section 505(b)(3)(B) and 355(j)(2)(B)(ii).) The proposed rule listed the type of information FDA considered necessary to enable patent owners to decide whether to sue for patent infringement. The list at proposed §§ 314.52(c) and 314.95(c) generated substantial debate, as reflected in the comments, as to the details to be included in a notice. The agency is neither prepared nor required to become involved in issues concerning sufficiency of notice for purposes of enforcing patent law. Therefore, FDA has revised both §§ 314.52(c) and 314.95(c) so that the detailed statement of the factual and legal basis behind the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed must include: (1) For each claim of the patent alleged not to be infringed, a full and detailed explanation why the claim is not infringed; and (2) for each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation. These provisions, as revised, paraphrase the statutory language. The sufficiency of the notice, for purposes of patent enforcement, is an issue to be resolved by the applicant and the patent owner or the holder of the approved application.

The agency has also revised §§ 314.52(c)(6) and 314.95(c)(6) by removing paragraphs (c)(6)(iii) entirely. FDA is making this change due to the numbers of comments that objected to the use of a "designated intermediary" and the "referee" concept in proposed §§ 314.52 and 314.95.

19. One comment would amend proposed § 314.52(e) pertaining to documentation of receipt of notice of certification of invalidity or noninfringement of a patent. The comment would include a signed receipt or delivery manifest as documentation of notice.

Section 314.52(e) clearly states that documentation of notice may be a copy of the return receipt or "other similar evidence of the date the notification was received." The provision also states that FDA will accept as adequate documentation of the date of receipt a return receipt or "a letter acknowledging receipt by the person provided the notice." Thus, § 314.52(e) does not limit an applicant to a particular form of documentation of notice. Applicants are required, however, to obtain agreement from FDA in advance if they intend to use a form of documentation other than return receipt.

20. The agency has also revised § 314.52(f) to state that the 45-day period provided for in section 505(c)(3)(C) of the Act will begin on the day following the date of receipt of the notice by the patent owner or its representative and by the approved application holder. The reasons for this change are described in comment 62 below.

The agency, on its own initiative, has also revised § 314.52(f) to state that the agency may begin the 45-day period on a later date if the applicant has amended its application to state that a later date should be used. This could occur, for example, where the applicant has amended its notice to the patent owner to provide more information regarding the applicant's notice of invalidity or noninfringement. This revision is also consistent with the corresponding provision for ANDA's.

C. Section 314.53—Submission of Patent Information

Proposed § 314.53 contained general requirements for the submission of patent information by NDA applicants

and NDA holders. For example, proposed § 314.53(b) would have required an NDA applicant to submit information on each patent that claims the drug or drug product for which the applicant is seeking approval or a method of using the drug that is the subject of the NDA or amendment or supplement and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Proposed § 314.53(c) described general reporting requirements, such as information on the type of patent and the name of the patent owner, and also required applicants to submit "certifications" with respect to formulation or composition patents (proposed § 314.53(c)(2)) and method of use patents (proposed § 314.53(c)(3)).

21. One comment addressed patent information and amendments of patent information under proposed §§ 314.50(h) and 314.53. These provisions would require each application under section 505(b) of the act to contain specific information about each patent that claimed the drug product or a method of using the drug product. The provisions also would require applicants to amend patent information or patent certifications and would permit the agency to disclose patent information. The comment said FDA should only publish patent information filed by NDA applicants at the time FDA approves the NDA.

A drug product does not necessarily have a patent by the time FDA approves the NDA. The statute expressly recognizes that a patent might issue after NDA approval, and, under such circumstances, instructs the NDA holder to file patent information within 30 days of the patent's issue date. Once FDA receives this information, the agency is obliged to publish it (see section 505(c)(2) of the act). Patent information might also change after NDA approval. For example, the patent term restoration provisions at 35 U.S.C. 156 give patent holders the opportunity to extend patent terms. The extended patent term may be as long as 5 years. However, patent owners cannot apply for patent term extension until FDA approves the product for marketing (see 35 U.S.C. 156(d)(1)). Thus, patent term restoration (also known as "patent term extension") always occurs after NDA approval, and patent owners who obtain such extensions usually notify FDA of the new patent expiration date. The new expiration date will be important to ANDA applicants because section 505(j)(2)(A)(vii) of the act requires ANDA applicants to submit patent certifications. Consequently, FDA does not accept the comment's suggestion.

22. One comment would amend proposed § 314.53 to establish a mechanism "for review of submitted patent information to determine, at least on a very general basis, applicability to the particular NDA in question."

FDA declines to adopt the comment. As stated elsewhere in this final rule, FDA does not have the expertise to review patent information. The agency believes that its scarce resources would be better utilized in reviewing applications rather than reviewing patent claims.

23. FDA, on its own initiative, has amended § 314.53(b) by replacing the phrase, "such patents consist of drug (ingredient) patents" with "such patents consist of drug substance (ingredient) patents." The final rule also replaces the phrase "For patents that claim a drug or drug product" with "For patents that claim a drug substance or drug product." These changes are intended to clarify the type of patents involved.

24. One comment would amend proposed § 314.53(b) by requiring an applicant to declare that it holds each patent or is the exclusive licensee of the patent owner or is authorized to submit patent information on behalf of the patent owner. The comment would also prohibit an applicant from submitting patent information and would prohibit the agency from listing any patent information if the applicant did not make any of these declarations.

The agency declines to amend the provision. Under § 314.53(c), the applicant must provide the name of the patent owner or, if the patent owner or applicant does not reside or have a place of business within the United States, the name of an agent or representative who resides or maintains a place of business within the United States and is authorized to receive notice of patent certification. Requiring an applicant to declare that it is the patent owner or exclusive licensee or is authorized to submit patent information would go beyond the statutory language at section 505(b)(1) of the act and would not serve any statutory purpose.

FDA also declines to amend the rule to prohibit the applicant from submitting patent information or to prohibit the agency from listing patent information without a declaration of ownership or license. Such an amendment would be contrary to section 505(b)(1) of the act and may result in less published patent information, thereby causing applicants to question the accuracy and validity of any patent information listed by FDA.

25. FDA received two comments that objected to proposed § 314.53(b) and (c) regarding the submission of patent information by NDA applicants. Both comments claimed that the 1984 amendments only require NDA applicants to provide patent numbers and patent expiration dates.

FDA disagrees with the comments. Section 505(b)(1) of the act requires an applicant to file "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application * * * and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." The requirement in § 314.53(b) and (c) that applicants provide information on the type of patent and the name of the patent owner or authorized representative is consistent with the purpose of section 505(b)(1) of the act.

26. One comment objected to proposed § 314.53(c)(2) and (c)(3). Proposed § 314.53(c)(2) would have required an applicant to provide a patent certification for each formulation or composition patent in addition to certain, general patent information. Proposed § 314.53(c)(3) would have required applicants to provide similar certifications for method of use patents. The comment said that a patent may contain formulation, composition, and method of use claims. The comment suggested deleting the proposed rule's classification of patents and replacing it with a general certification that the patents listed by the applicant contain claims with respect to which the applicant could reasonably assert a claim of infringement against a person engaged in the unlicensed manufacture, use, or sale of the drug for which the application was submitted.

FDA acknowledges that a patent may contain a variety of claims, and has revised proposed § 314.53(c)(2) by creating a single certification statement. The new certification statement would have an applicant state that, "The undersigned declares that Patent No. _____ covers the formulation, composition, and/or method of use of (*name of drug product*). This product is (*currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act*) [or] (*the subject of this application for which approval is being sought*): _____." However, because section 505(b)(1) of the act specifically requires applicants to "file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which

claims a method of using such drug," and because FDA lacks patent law expertise, the agency strongly encourages applicants to identify, to the best of their ability, the type of patent covering the drug or drug product. This information will help FDA determine which claims cover the drug or drug product and which claims cover a method of use.

27. One comment said FDA should not list formulation patents. Proposed § 314.53(c)(2) would require applicants under section 505(b) of the act to provide information on formulation or composition patents, and FDA would publish this information under § 314.53(e). The comment said this would increase the number of generic drug applications by avoiding difficult questions of exclusivity for "patentably distinct formulations" and noted that patent owners can always resort to patent law to halt possible patent infringement.

FDA disagrees with the comment. The statute expressly requires applicants to file "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application * * *" (section 505(b)(1) of the act). Thus, if the formulation patent claimed the drug product in the application, the applicant must file information on that patent.

28. One comment would revise proposed § 314.53(c)(2)(i), (c)(3)(i), and (c)(4) to refer to a "declaration" rather than "certification." The comment explained that the 1984 amendments used the word "certification" with respect to patent information to be submitted by applicants under section 505(b)(2)(A) and (j)(2)(A)(vii) of the act, so use of the word "certification" in proposed § 314.53(c) would be confusing.

The agency agrees and has revised these and other sections of the rule accordingly.

29. One comment would delete proposed § 314.53(c)(2)(ii) and (c)(3)(ii). The comment said that the provision for the correction of patent information at proposed § 314.53(f) would ensure that patent information is correct.

The provisions cited by the comment serve different purposes. As revised, § 314.53(c)(2)(ii) requires an applicant to provide patent information about a product within 30 days after the date of approval; these provisions contemplate the possibility that the patents pertaining to a product's formulation, composition, and uses may change between the time the application is initially submitted and the time the application is approved (see 54 FR 28872 at 28909). Although § 314.53(f) enables any person to dispute the accuracy or relevance of the patent information submitted to FDA, it is the responsibility of the applicant, not the general public or the applicant's competitors, to ensure that the information provided by the applicant is accurate. These provisions for amending patent information are necessary for maintaining an accurate list of patent information and useful for applicants who must comply with the patent certification requirements. Therefore, FDA declines to adopt the comment.

30. FDA received two comments on proposed § 314.53(c)(4) (now renumbered as § 314.53(c)(3)), which would enable an applicant to claim that there are no relevant patents that claim the drug product or a method of using the drug product. One comment supported the provision; the other recommended deleting it entirely, stating that the only party that would be injured by the failure to list a patent is the NDA applicant.

FDA declines to delete the provision as suggested. The agency disagrees with the assertion that the NDA applicant would be the only party injured by the failure to list a patent. The patent holder may be a person other than the NDA applicant and may be injured if the patented invention is made, sold, or used without the patent owner's knowledge or consent. Failure to list a patent may also result in injury to other applicants who devote resources towards submitting applications for duplicate products without realizing that those products may be covered by the patent.

31. FDA, on its own initiative, has reorganized § 314.53(d) to clarify further when and where patent information should be submitted. As revised, § 314.53(d)(1) pertains to patent information requirements for original applications. New § 314.53(d)(2), formerly § 314.53(d)(2)(ii), applies to patent information requirements for supplements, and a new § 314.53(d)(3), formerly § 314.53(d)(2)(i), applies to patent information submitted after an application has been approved. The agency has renumbered the remaining paragraphs accordingly.

32. Proposed § 314.53(d) instructed applicants when and where to submit patent information in an original application and in a supplement and would require an applicant to provide patent information within 30 days if a patent issues for a drug, drug product, or method of use after the application had been approved. Three comments asked FDA to extend the 30-day period in proposed § 314.53(d) to 60 days.

FDA declines to accept the comment. The 30-day period is consistent with section 505(c)(2) of the act and permits the agency to include the latest patent information in supplements to the Orange Book. If FDA provided for a longer time period, the Orange Book and its supplements might be less likely to contain current patent information for each product, and potential applicants might be misled by outdated patent information. FDA has, on its own initiative, clarified § 314.53(d)(1) and (d)(3) to mention the 30-day deadline.

33. Proposed § 314.53(d)(2)(ii) (now renumbered as § 314.53(d)(2)) would require an applicant to submit patent information for a patent that claims the drug, drug product, or a method of using the product if the applicant sought approval of certain, listed changes through a supplemental application. One comment would revise proposed § 314.53(d)(2)(ii) to require an applicant to provide a patent declaration for each supplement. The comment explained that this would "eliminate the risk that the four types of supplements described in the proposal do not comprise the entire universe of supplements that may affect the patent information filed with the FDA." The comment would also require an NDA applicant to submit information on patents that claim the formulation or composition each time the NDA applicant submits a supplement to revise the formulation or composition.

FDA disagrees with the comment. Section 505(b)(1) of the act requires an applicant to submit information on each patent that claims the drug or a method of using a drug product for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. The supplements listed in new § 314.53(d)(2)(i)—supplements to change a formulation, to add a new indication or other condition of use, to change the strength, or to make any other patented change regarding the drug, drug product, or any method of use—are those that concern the drug product or a method of using the drug product. Additionally, new § 314.53(d)(2)(i)(D) provides for the submission of patent information for any other type of patented change. Requiring an applicant to provide patent information for all supplements, even if the supplement did not involve a change to the drug product or a method of using the product (i.e., a change in the site of manufacturing), would increase the workload on applicants and the agency without a significant benefit.

The suggestion that FDA require an applicant to submit information on patents that claim the formulation or composition each time the NDA applicant submits a supplement to revise the formulation or composition is apparently based on a misreading of proposed § 314.53(d)(2)(ii)(A) (now renumbered as § 314.53(d)(2)(i)(A)). This section already requires an applicant to provide such information. Thus, the comment's suggestion is unnecessary.

34. One comment would revise proposed § 314.53(d)(2)(ii)(D) (now renumbered as § 314.53(d)(2)(i)(D)) to require the submission of patent information if the applicant submits a supplement to make any other patented change "except patented manufacturing processes."

The suggested revision is unnecessary because § 314.53(b) clearly states that, "Process patents are not covered by [§ 314.53] and information on process patents may not be submitted to FDA."

35. One comment would delete proposed § 314.53(d)(2)(v) (now renumbered as § 314.53(d)(2)(iv)), which would require an applicant to comply with the requirements for amending formulation, composition, or method of use patent information. The comment said applicants are already required to comply with such requirements.

FDA disagrees with the comment. Section 314.53(d)(2)(iv) requires applicants to amend the patent information to account for changes proposed in supplemental applications whereas § 314.53(c)(2)(ii) and (d)(2)(ii) require an applicant to amend patent information when there have been changes in status, or there is other new information regarding the relevant patents.

36. Proposed § 314.53(d)(3) (now renumbered as § 314.53(d)(4)) would require an applicant to submit two copies of each submission of patent information. One copy would go to the archival copy of the application and the other copy would go to the chemistry, manufacturing, and controls section of the review copy. One comment would delete the phrase "of the review copy" from proposed § 314.53(d)(3) on the grounds that the phrase appeared to be a typographical error.

FDA believes that the comment misreads proposed § 314.53(d)(3). An applicant is required to submit an archival copy and a review copy of an application consisting of several separately bound technical sections. New § 314.53(d)(4) requires an applicant to provide two copies of each submission of patent information. One copy will go to the archival copy of the NDA; the other will go to the chemistry, manufacturing, and controls technical section of the review copy of the NDA.

37. FDA, on its own initiative, has amended § 314.53(e) regarding public disclosure of patent information. As originally proposed, § 314.53(e) stated that, for each use patent, FDA would publish the "approved indications or other conditions of use covered by a patent and any unapproved indications or condition of use to which the applicant certified." The agency is deleting the reference to "any unapproved indications or condition of use" to be consistent with the patent information requirements in § 314.53(c).

38. FDA received two comments on proposed § 314.53(f) regarding corrections of patent information errors. The proposed provision would require a person disputing the accuracy or relevance of patent information submitted to and published by FDA to first notify the agency in writing stating the grounds for the disagreement. The agency would then ask the NDA holder to confirm whether the patent information was correct, but would not change the patent information listed in the Orange Book unless the NDA holder withdrew or amended that information. If the NDA holder did not change the patent information, a 505(b)(2) applicant or ANDA applicant would be required to make a certification for the listed patent despite any disagreement as to its correctness.

Both comments said that FDA should ensure that patent information submitted to the agency is complete and applies to a particular NDA. One comment would also amend the rule to have FDA confirm, upon request from any person, the accuracy or relevance of the patent information submitted to the agency. One comment said the agency should not provide applicants the grounds for a disagreement on the accuracy or relevance of patent information.

As stated elsewhere in this rule, FDA does not have the resources or the expertise to review patent information for its accuracy and relevance to an NDA. Therefore, the agency declines the comment's requests to ensure that patent information is complete and relevant to an NDA and to confirm, upon request, the validity of patent information submitted to the agency. The agency believes that the declaration requirements under § 314.53(c), as well as an applicant's potential liability if it submits an untrue statement of material fact, will help ensure that accurate patent information is submitted.

FDA also declines to amend the rule to prevent the agency from providing applicants the grounds for a disagreement on the accuracy or relevance of patent information. Absent such information, a patent owner will be unable to evaluate the disagreement or to explain whether the patent information is correct.

39. One comment noted that proposed § 314.53(f) does not require applicants to correct patent listings. The comment would revise the provision to permit applicants to "make otherwise pertinent certifications while a listing dispute is pending." The comment would also require FDA to notify the NDA holder of the disagreement within 15 days of notification and require patent owners or NDA holders to respond to a disagreement on patent information or to withdraw or amend the patent information within 30 days. The comment would then require FDA to immediately send the NDA holder's response to the party that began the disagreement and inform the party whether the patent would remain listed.

As originally proposed, § 314.53(f) expressly required an applicant to make "an appropriate certification for each listed patent" notwithstanding any disagreement as to the correctness of the listed patent information. If, as FDA assumes, the proposed reference to "otherwise pertinent certifications" means "appropriate certifications," the proposal is unnecessary. If the proposed reference is to negate any responsibility to file an appropriate certification for a patent that is subject to a dispute over listing, FDA rejects the proposal. Until the dispute is resolved, the patent is listed within the meaning of the act. FDA also declines to amend the rule to impose deadlines for resolving patent disagreements. The agency believes that such deadlines would be impractical, considering the agency's lack of expertise in patent matters and the volume of applications FDA receives, and agency resources would be better spent on reviewing applications rather than exchanging disputed patent information among parties as proposed by the comment. The agency also notes that it has not had any significant problems with the informal procedures described in proposed § 314.53(f) as most NDA holders have amended or corrected their patent information after FDA has informed them of a dispute.

The agency has, however, revised § 314.53(f) to provide a new address for the submission of written statements disputing the relevance or accuracy of patent information. Such statements should now be directed to the Drug Information Services Branch in the Division of Drug Information Resources.

This change reflects current FDA operations.

D. Section 314.54—Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication for, or Other Change From, a Listed Drug

Proposed § 314.54(a)(1)(vii) would require an applicant seeking approval of a drug product that represents a modification of a listed drug, to provide certain information regarding marketing exclusivity if the applicant believed the modification would be entitled to such exclusivity.

The agency received no comments on this provision and has finalized it without change.

E. Section 314.70—Supplements and Other Changes to an Approved Application

Proposed § 314.70(e) (now renumbered as § 314.70(f)) would require applicants submitting a supplement to an approved application to provide certain marketing exclusivity information if the applicant intended to seek market exclusivity.

The agency received no comments on this provision and has finalized it without change.

F. Section 314.94—Content and Format of an Abbreviated Application (21 CFR 314.94)

Proposed § 314.94(a)(12) contained the patent certification requirements for ANDA's. For example, under proposed § 314.94(a)(12)(i), an ANDA applicant would provide a patent certification with respect to each patent that claims the reference listed drug or that claims a use of the reference listed drug for which the ANDA applicant is seeking approval. Proposed § 314.94(a)(12)(ii) would permit an ANDA applicant to certify that there are no relevant patents that claim the listed drug or a method of use of the listed drug. Proposed § 314.94(a)(12)(iii) would permit an ANDA applicant to state that the use for which the applicant is seeking approval is not covered by a patent claiming a use for the listed drug.

40. One comment claimed that proposed § 314.94(a)(12)(i)(A) was inconsistent with the statute because the statute only requires ANDA applicants to make certifications for listed patents rather than patents issued by the United States Patent and Trademark Office. Two comments added that the suggestion regarding patent searches that FDA made in the preamble to the proposed rule was irrational and legally insupportable. One company, however, agreed that ANDA applicants should submit patent certifications with respect to all patents, including those that had not been submitted to FDA for listing.

The rule simply paraphrases the statutory language in section 505(j)(2)(A)(vii) of the act. The rule does not require ANDA applicants to conduct patent searches. If the applicant believes that no patent exists, the applicant is to submit a patent certification under § 314.94(a)(12)(ii) that no relevant patents exist. If the applicant believes that a patent exists but that the patent owner has not filed patent information at FDA, the ANDA applicant would certify that, "in its opinion and to the best of its knowledge," no patent information has been submitted (i.e., make a paragraph I certification). FDA, however, believes it would be prudent for applicants to conduct patent searches if possible. A patent search could reveal the existence of an unlisted, but valid, patent and thus prevent an unnecessary expenditure of resources by applicants and FDA on a product that might not be marketable. A patent search might also enable ANDA applicants to avoid unnecessary patent infringement litigation.

41. One comment suggested that FDA publish all patent information, including descriptions of the patents and patent numbers, in the Orange Book.

The Orange Book already contains an addendum listing both patent and exclusivity information. This section provides patent numbers and patent expiration dates as well as exclusivity codes and expiration dates. In addition, for a use patent, FDA includes in the Orange Book a code identifying the indication covered by the patent. As for patent descriptions, FDA lacks the expertise to review and summarize patents and individual patent claims and does not believe that expanding the Orange Book to include patent descriptions would be an efficient use of FDA resources. However, persons who wish to obtain a synopsis of a particular patent can consult the Official Gazette for Patents, which is published by the United States Patent and Trademark Office. The Official Gazette for Patents contains short descriptions of patents and is publicly available.

42. One comment asserted that FDA should list patents that claim drug products for which the patent owner is not seeking or has not obtained approval. The comment explained that the statute requires NDA holders and applicants to submit information on "any patent which claims the drug for which the applicant submitted the application" (section 505(b)(1) of the act). The comment, citing § 314.50(d)(1), claimed that "drug" means the active ingredient while "drug product" denotes a marketed product composed of active and inactive ingredients. Thus, because section 505(b)(1) of the act uses the term "drug," the comment continued, any patent that claims the active ingredient is a patent that claims the drug for which the applicant submitted the application and should be listed.

FDA disagrees with the comment's interpretation of section 505(b)(1) of the act. The statutory provision states that patent information is to be filed on patents that claim the drug "for which the applicant submitted the application." Similarly, the House Report accompanying the Drug Price Competition and Patent Term Restoration Act indicates that the patent information to be filed "includes the patent number and the expiration date of any patent which claims the drug *in the NDA* or which claims *a method of using such drug* with respect to which a claim of patent infringement could reasonably be asserted * * *." H. Rept. 857, 98th Cong., 2d sess. 31–32 (1984) (emphasis added). Thus, both the statute and its legislative history reveal that Congress intended the term "drug" to mean "drug product" rather than "active ingredient" because NDA's are granted only for drug products and not for active ingredients. FDA's interpretation of this provision has been upheld by a United States magistrate in *Pfizer* v. *FDA*, No. HM–88–1019, slip op. at 10–13 (D. Md. October 2, 1989) and adopted by a Federal district court (see *Pfizer, Inc.* v. *Food and Drug Administration*, 753 F.Supp. 171 (D. Md. 1990)).

43. Several comments sought clarification regarding the interaction between proposed § 314.94(a)(12)(i)(A)(*4*) and § 314.94(a)(12)(v), 180-day exclusivity periods under section 505(j)(4)(B)(iv) of the act, and licensees.

Because patent licensees are subject to 180-day exclusivity that has been granted to another applicant, the only instance in which proposed § 314.94(a)(12)(v) would apply would be where a patent licensee would seek to have an effective approval of its ANDA or 505(b)(2) application within 45 days of its receipt or filing (because the patent holder has 45 days to file a lawsuit against an ANDA applicant making a paragraph IV certification). Because the agency does not anticipate approving an ANDA or 505(b)(2) application in 45 days, FDA, on its own initiative, removed the provisions in § 314.94(a)(12)(v) and § 314.107(b)(1)(iv) related to consent by a patent owner to

an immediate effective date of approval for a licensee.

44. Two comments disagreed with proposed § 314.94(a)(12)(ii), which would require ANDA applicants to certify that there are no relevant patents that claim the listed drug referred to in the ANDA. One comment said that ANDA applicants should only be required to certify that no listed patents claim the listed drug referred to in the ANDA. The second comment suggested deleting the provision and revising proposed § 314.94(a)(12)(i)(A)(*1*) so ANDA applicants would certify that no patent information had been filed.

FDA declines to accept the comments. As stated in the preamble to the proposed rule, an applicant makes a patent certification under § 314.94(a)(12)(ii) if "in the applicant's opinion and to the best of its knowledge, no relevant patents claim the listed drug or a method of using the listed drug" (54 FR 28872 at 28885). The applicant makes the patent certifications under § 314.94(a)(12)(i) when it is aware of or believes that a patent covers the listed drug. (Id.) FDA believes that § 314.94(a)(12)(ii) will enable FDA to ensure that each applicant has complied with the patent certification requirements.

45. One comment asked FDA to define "relevant" for proposed § 314.94(a)(12)(ii). The word "relevant" refers to those patents defined by section 505(j)(2)(A)(vii) of the act for which a patent certification would be required, i.e., patents that claim the listed drug, or drug substance component thereof, referred to in the ANDA or that claim a use of the listed drug or drug substance for which the ANDA applicant seeks approval and for which patent information is required to be filed under section 505 (b) and (c) of the act and § 314.53.

Although patents that are held to be invalid or unenforceable in a judicial decision may be removed from the list by FDA, a patent that has been declared invalid or unenforceable in a lawsuit resulting in 180-day exclusivity will be deemed relevant under § 314.94(a)(12)(ii) and will not be removed from the list until the end of the 180-day exclusivity period. This will ensure that 180-day exclusivity cannot be avoided by changing a patent certification.

46. Several comments objected to proposed § 314.94(a)(12)(iii), which would require ANDA applicants to provide a patent statement if the listed patent is for a method of use and that applicant does not intend to claim any of the patented uses. The comments recommended that such ANDA applicants certify, under § 314.94(a)(12)(i)(A)(*4*), that the listed use patent would not be infringed, thereby giving the patent owner notice of possible patent infringement. One comment asked how proposed § 314.94(a)(12)(iii) would affect eligibility for the 180-day exclusivity period. The comment explained that the statute requires ANDA applicants to make patent certifications under section 505(j)(2)(A)(vii) of the act and statements for method of use patents under section 505(j)(2)(A)(viii) of the act. However, the comment stated, for method of use patents, the proposed rule could be interpreted as giving ANDA applicants the option of making a patent certification of noninfringement under proposed § 314.94(a)(12)(i)(A)(*4*) or a statement that the applicants' drug products do not involve a patented claim under proposed § 314.94(a)(12)(iii).

FDA does not intend § 314.94(a)(12)(i)(A)(*4*) to authorize certifications with respect to patents that claim a use for the listed drug for which the applicant is not seeking approval. The statute requires patent certifications only if the patent "claims a use for [the] listed drug for which the applicant is seeking approval * * *" (section 505(j)(2)(A)(vii) of the act). The statute requires an applicant to make a patent statement when a method of use patent "does not claim a use for which the applicant is seeking approval * * *" (section 505(j)(2)(A)(viii) of the act).) The proposed rule recognized this distinction. FDA stated that if a patent claims a method of using the listed drug, and labeling for the ANDA applicant's proposed drug product does not contain any indications covered by the method of use patent, the ANDA applicant "should not submit a certification under § 314.94(a)(12)(i)(A) for such a patent" (54 FR 28872 at 28886). The preamble also indicated that if the labeling for the ANDA applicant's product did contain an indication that was claimed by a patent, the applicant should make a certification under § 314.94(a)(12)(i)(A). (Id.) Thus, the two provisions cited by the comment are not overlapping, and an applicant does not have the option of making a certification under § 314.94(a)(12)(i)(A)(*4*) in lieu of, or in addition to, a statement under § 314.94(a)(12)(iii).

If, however, there are listed patents that present both a product and method of use claim, the applicant may file a paragraph IV certification with respect to the product patent or patent claim and a statement that the product that is the subject of the application does not involve a patented method of use with respect to the method of use patent or patent claim.

47. One comment recommended revising proposed § 314.94(a)(12)(v) to provide NDA holders the opportunity to consent to licensing agreements between ANDA applicants and patent owners. As written, proposed § 314.94(a)(12)(v) did not address this issue.

Neither the statute nor the legislative history suggests that NDA holders should be given such a right, and the agency is not prepared to infer such a right to interfere in the patent holder's enjoyment of its right to license. However, as stated earlier, FDA has elected to remove the language in § 314.94(a)(12)(v) regarding consent by the patent owner.

48. One comment objected, in part, to proposed § 314.94(a)(12)(vi), which would require an ANDA applicant to provide a patent certification in response to an untimely submission of patent information if the ANDA was submitted after the untimely submission of patent information or did not contain an appropriate patent certification at the time the patent information was submitted. The comment correctly noted that FDA may refuse to approve or may even withdraw approval of an application for failure to submit patent information (see section 505 (d)(6) and (e)(4) of the act). The comment said these sanctions emphasize the importance of filing patent information, and FDA "should not provide any benefit to the NDA applicant who ignores the statutory requirement for timely submission of such information."

Section 314.94(a)(12)(vi) is intended to effectuate Congress' intent to enforce timely submission of patent information. As discussed more fully in the response to comment 7 above, FDA believes a less severe sanction than the withdrawal of NDA approval for late submission of patent information would ordinarily effectuate congressional intent. For the reasons discussed in response to comment 7 FDA has concluded that if an NDA applicant submits required patent information on an approved drug product more than 30 days after issuance of the patent, the agency will publish the untimely information but will not require ANDA applicants with pending applications who have previously submitted a certification that was correct at the time it was submitted, i.e., those applicants who would be prejudiced by the late submission, to recertify as to the new patent. Applicants who initially submit ANDA's after the submission of the patent information or whose pending

applications do not contain a valid certification at the time of the submission would be required to submit a certification as to that patent. The agency, therefore, declines to revise this provision.

FDA also notes that, if an ANDA applicant with a pending application voluntarily makes a patent certification for an untimely filed patent, the ANDA applicant may withdraw the patent certification for the untimely filed patent. The agency, on its own initiative, has amended § 314.94(a)(12)(viii) to make this clear. Additionally, if the patent certification for the untimely filed patent was a paragraph IV certification (claiming that the patent is invalid or would not be infringed), the agency would not consider the withdrawn paragraph IV certification to preclude FDA from granting 180-day exclusivity to another ANDA applicant.

49. Proposed § 314.94(a)(12)(vii) would permit an ANDA applicant to seek confirmation of the correctness of patent information, but would also require an ANDA applicant to submit the appropriate patent certification if the disputed patent information was not amended or withdrawn. One comment suggested amending proposed § 314.94(a)(12)(vii) to declare the end of the error correction process for patent information to be final agency action. The comment explained that this section permits challenges to listed patents but, in conjunction with proposed § 314.53(f), neglects to contain a process to require patent owners to withdraw or modify patent listings. The comment said that declaring the end of the error correction process to be final agency action would enable ANDA applicants to seek judicial review rather than wait for the patent owner to voluntarily correct the patent information.

FDA disagrees with the comment. Disputes between ANDA applicants and patent holders regarding the validity or correctness of the listed patent information must be resolved among the ANDA applicants and the patent holders rather than by agency action. FDA stated this position in the preamble to the proposed rule (see 54 FR 28872 at 28910).

50. One comment addressed proposed § 314.94(a)(12)(viii) and asked FDA to permit applicants to amend their patent certifications if a patent is declared invalid. The comment proposed that any amendment, with the exception of a paragraph IV certification being changed to a paragraph III certification, be considered nunc pro tunc (now for then). If a patent were declared invalid, the comment suggested that an amendment from paragraph IV to paragraph III be considered "as if a III were originally filed, subject to a prior IV certificant's exclusivity rights during the remaining lifetime of the patent." Finally, the comment said that applicants should be permitted to make a paragraph I certification if the patent were removed from the list.

FDA agrees in part with the comment. An applicant may change its certification at any time. Although there is no need for the agency to pronounce such changes in certification nunc pro tunc, the agency agrees that the protection offered by 180-day exclusivity should not be undermined by changes from paragraph IV certification or by the filing of original certifications other than paragraph IV certifications. If a patent were removed from the list immediately upon a court decision that the patent is invalid or unenforceable, an applicant with a subsequently filed application might seek to certify that there is no relevant patent and seek an immediately effective approval. To ensure that this does not occur, the agency has required that a patent remain on the list after being declared invalid or unenforceable until the end of any applicable 180-day exclusivity period. This means that a patent is deemed to be relevant under § 314.94(a)(12)(ii) until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first. Thus, where there is a patent that has been challenged by a paragraph IV applicant, a subsequent applicant will not be able to file a certification that there is no relevant patent or seek an immediately effective approval until either the patent or the 180-day exclusivity period expires. The agency has amended § 314.94(a)(12)(viii)(B) and made a similar change to § 314.50(i)(6)(ii) to reflect this position.

The agency also notes that an applicant may withdraw its patent certification at any time. However, as stated earlier, if an ANDA applicant made a paragraph IV certification and later withdraws that certification, the agency will not regard the withdrawn paragraph IV certification as precluding the agency from granting 180-day exclusivity to a subsequent ANDA applicant.

51. One comment suggested that ANDA applicants amend their patent certifications to a paragraph I certification if FDA or the NDA holder "delists" a patent.

As stated in the preamble to the proposed rule, the agency believes that a certification under § 314.94(a)(12)(ii), stating that no relevant patents claim the listed drug, would be more appropriate if a patent is "delisted" (see 54 FR 28872 at 28886).

52. One comment asked FDA to clarify proposed § 314.94(a)(12)(viii)(A) so that an amended patent certification would be required if a patent were held valid and infringed but not required if a patent were held infringed, but not valid.

If a claim is found to be invalid or unenforceable, the patent will ordinarily be removed from the list, and applicants with pending applications containing certifications with respect to that patent must amend their certifications accordingly to certify that no relevant patents claim the drug or, if another relevant patent claims the drug, to make an appropriate certification regarding that patent. In the amendment, the applicant must state the reason for the change in certification (that the patent has been removed from the list). A patent that is the subject of a lawsuit under § 314.107(c) will not be removed from the list until FDA determines either that no delay in effective dates of approval is required as a result of the lawsuit or that any such period of delay in effective dates of approval is ended. The agency has amended § 314.94(a)(12)(viii)(B) to clarify its position regarding certifications and patents removed from the list.

The agency also advises applicants to submit any patent certification changes by letter if the applicant has not received a "not approvable" letter from the agency. If the applicant has received a "not approvable" letter, it may include the amended certification along with the complete response to the deficiencies in the "not approvable" letter. This will enable FDA to process amendments more efficiently.

53. Six comments addressed amended certifications under proposed § 314.94(a)(12)(viii)(C)(*2*) which would not require applicants to amend their patent certifications when patent information is submitted after the abbreviated application's approval "whether or not the approval of the abbreviated application is effective." One comment would require amended patent certifications only if a new patent issued after the ANDA had been submitted and make supplements optional after ANDA approval. Five comments would require ANDA applicants to amend patent certifications until the effective date of their ANDA approvals because the existence of a patent would affect the ANDA's effective date of approval.

In the **Federal Register** of April 28, 1992 (57 FR 17950 at 17953), FDA stated that it had clarified its policies

with respect to drug products with delayed effective dates of approval. The agency stated that an approval with a delayed effective date is tentative and does not become final until the effective date. Therefore, FDA has amended § 314.94(a)(12)(viii)(C)(2) by deleting the phrase "whether or not the approval of the abbreviated application is effective," and, consistent with this change, and in response to the comments, by requiring an ANDA applicant to amend its patent certifications until the effective date of ANDA approval.

G. Section 314.95—Notice of Certification of Invalidity or Noninfringement of a Patent

Proposed § 314.95 described an ANDA applicant's obligations with respect to a notice of certification of invalidity or noninfringement of a patent. Proposed § 314.95(a), for example, would require an ANDA applicant to provide notice to the patent owner and the NDA holder. Proposed § 314.95(b) would require an ANDA applicant to send the notice when it receives an acknowledgment letter from FDA stating that the ANDA is sufficiently complete for review to begin. Proposed § 314.95(c) prescribed the contents of a notice of certification of invalidity or noninfringement of a patent, including "a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed."

54. One comment recommended that FDA revise the regulation by adding a mechanism whereby FDA or the United States Patent and Trademark Office would review notices of certification of invalidity or noninfringement. The comment would have FDA suspend the 45-day period provided by section 505(j)(4)(B)(iii) of the act until FDA or the United States Patent and Trademark Office determined that the notice was sufficient.

FDA declines to adopt the comment. As stated elsewhere in this preamble, FDA lacks expertise in patent law. Moreover, neither FDA nor the United States Patent and Trademark Office currently has access to the additional resources that would be necessary to review these notices, and a patent certification review system would subject the agency's decisions to questioning that would require further resource expenditures and create delays in the statutory patent certification and challenge process.

The agency does note, however, that in cases where the notice was deemed inadequate by the patent owner or exclusive patent licensee and where the ANDA applicant subsequently amends the notice, the agency may, if the applicant amends its ANDA with a written statement that the date of receipt of the amended notification should be considered the date of receipt of notice, use the date of the amended notification to begin the 45-day statutory period for institution of an action for patent infringement (see 54 FR 28872 at 28888; see also § 314.95(f)).

55. Two comments addressed return receipts under proposed § 314.95(a). One comment would amend the rule to provide for signed receipts while the second would revise the rule to permit reliance on "any appropriate federal rule for transmitting notice to another party or for receipt of such notice."

Under § 314.95(e), applicants are required to document receipt of a notice of invalidity or noninfringement by submitting "a copy of the return receipt or other similar evidence of the date the notification was received." The rule states that FDA will accept return receipts, letters acknowledging receipt by the person provided the notice, or "another form of documentation only if FDA has agreed to such documentation in advance." Thus, the rule provides several methods for documenting receipt of a notice, so the comment's recommendations are unnecessary.

56. One comment asked FDA to clarify when multiple notices might be required.

Section 314.95(a) requires applicants to send notices to each patent owner and each holder (or its attorney, agent, or other authorized official) of the approved application under section 505(b) of the act for the listed drug that is claimed by the patent and for which the applicant is seeking approval (§ 314.95 (a)(1) and (a)(2)). Consequently, applicants could be obliged to send multiple notices under several situations. For example, a patent owner is usually an individual whereas the holder of an approved application is often a corporation. The applicant, therefore, would send one notice to the patent owner and another to the firm holding the approved application. If several patents cover the listed drug, there may be several different patent owners, so the applicant would be required to provide separate notices to each patent owner.

57. Two comments suggested revising proposed § 314.95(a)(1) to include the patent owner's name and address in the Orange Book.

The patent owner's name and address are printed on each patent. As a result, whenever a prospective applicant examines a patent to determine whether its proposed product would infringe any of the patent claims, the applicant would have access to the patent owner's name and address. The comment's suggestion, therefore, is unnecessary.

58. Several comments asked when and how applicants should send notices under proposed § 314.95(b). Two comments would have an applicant provide a statement to FDA declaring that the applicant "will give," rather than "has provided," notice of certification of invalidity or noninfringement of a patent. These comments explained that the statute does not specify a time for the notice, so the rule should permit applicants to decide when to send such notices. One comment would revise the rule to give FDA 30 days to determine whether the ANDA was complete before the applicant would be required to send a notice of certification of invalidity or noninfringement of a patent.

The legislative history discussing a notice of certification of invalidity or noninfringement of a patent clearly states that ANDA applicants should provide notice "simultaneously with the submission of an ANDA" and that Congress did "not intend that applicants be permitted to circumvent this notice requirement by filing sham ANDA's or ANDA's which are substantially incomplete" (see H. Rept. 857, 98th Cong., 2d sess. 24 (1984)). Thus, to permit applicants to state that they "will provide" notice to the patent owner and holder of the approved application would be contrary to congressional intent. Moreover, such a statement would be redundant relative to that required under § 314.94(a)(12)(i) and would not inform FDA whether notice has, in fact, been provided. With regard to the suggestion of a 30-day deadline for FDA to respond before an applicant sends notice, FDA believes such a requirement would be impractical. The time required to review an application may vary depending upon the application's complexity, the review division's workload, the timing and scope of an applicant's response to FDA's questions or requests, etc. Although FDA intends to review applications expeditiously, current resources and priorities may not, in all instances, enable the agency to determine whether an application is sufficiently complete for review to begin within 30 days after receiving the application. Consequently, FDA declines to adopt the comments.

59. One comment argued that proposed § 314.95(b) creates a delay that is detrimental to ANDA applicants and is contrary to the 1984 amendments and the legislative history. The comment said that proposed § 314.95(b) would deprive ANDA applicants of "statutory

rights" associated with the 45-day period and the 30-month period for the effective date of an ANDA approval and could present problems among competing ANDA applicants. The comment said FDA should permit ANDA applicants to provide notice upon submission of an application or have ANDA applicants await an initial FDA determination (presumably as to whether the application is received) before providing notice.

FDA disagrees with the comment. As stated above, the legislative history expressly states that notice of certification of invalidity or noninfringement of a patent must be given simultaneously with the submission of an ANDA and that the ANDA cannot be a "sham" ANDA or one that is substantially incomplete (see H. Rept. 857, 98th Cong., 2d sess. 24 (1984)). As written, § 314.95(b) is consistent with the legislative history because it requires the ANDA applicant to provide notice once FDA has determined that the ANDA is substantially complete to permit a substantive review. To permit an ANDA applicant to provide notice before FDA has determined whether the ANDA is sufficiently complete would be contrary to the legislative history because it would only encourage ANDA applicants to file incomplete or "sham" ANDA's and to supplement them later to secure a place in the review queue in an attempt to secure the first ANDA approval.

60. FDA received five comments regarding the exact contents of a notice of certification of invalidity or noninfringement of a patent. Two comments would revise the rule to require applicants to disclose all components, including active and inactive ingredients, in the applicant's prospective formulation, the proportions of those components, and all grounds supporting the applicant's assertion that the patent is invalid or will not be infringed. Three comments opposed disclosure of the applicant's formulation or composition information or a detailed statement of the applicant's legal reasoning. These comments explained that such information and statements might compromise the applicant's trade secrets and adversely affect the applicant's ability to engage in litigation.

As noted above in comment 18, the agency did not anticipate that the list in proposed § 314.95(c) would generate the debate reflected in the comments and, again, reiterates that the agency does not have the expertise or the desire to become involved in issues concerning patent law and sufficiency of notice. Therefore, FDA has revised § 314.95 to require that the detailed statement of the factual and legal basis behind the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed include the following: (1) For each claim of a patent alleged not to be infringed, a full and detailed explanation why the claim is not infringed; and (2) for each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation (see §§ 314.52(c)(6)(i) and (c)(6)(ii) and 314.95(c)(6)(i) and (c)(6)(ii)). Disputes involving the sufficiency of the notice must be resolved by the applicant, patent owner, and holder of the approved application rather than by action on the part of FDA.

61. FDA also received five comments opposing the use of a referee or designated intermediary under proposed § 314.95(c)(6)(iii). The proposal would have required an ANDA applicant to describe a mechanism for disclosing the formulation or composition of the proposed drug product to the patent owner or to a "designated intermediary who will act as a referee" on the subject of patent invalidity or noninfringement. The comments said that the concept was legally unauthorized and interfered with the traditional judicial process for resolving patent disputes.

FDA agrees that traditional processes for resolving patent disputes, which do not involve the agency's regulations, are appropriate under these circumstances. Therefore, the agency has deleted the provision in its entirety.

62. Proposed § 314.95(f) would presume a notice of certification of invalidity or noninfringement to be complete and sufficient if the ANDA applicant complied with the regulatory requirements under § 314.95(a) through (e) and would start the 45-day clock for filing a patent infringement suit on the date following receipt of the notice. One comment challenged the presumption that a notice is complete and sufficient to permit the statutory 45-day period to begin. The comment would revise the rule to require applicants to file a complete copy of the certification and notice of service with FDA and delay the start of the 45-day period if any dispute over the certification's sufficiency arose. A second comment argued that an approved application holder who is also an exclusive patent licensee might have different interests than the patent owner. The comment would revise the rule to require notice to both the patent owner and to the licensee or approved application holder.

With respect to FDA's presumption that a notice is complete and sufficient to begin the 45-day period, § 314.95(c), as amended, paraphrases the statutory language concerning notices and does not attempt to establish more detailed requirements for "sufficiency" of a notice. FDA has revised § 314.95(f) to state that it will begin the 45-day period on the first day after the documented date of receipt by the person(s) receiving the notice. FDA will be able to determine this date because § 314.95(e) requires applicants to submit documentation of receipt of notice. FDA may, if the applicant amends its ANDA with a written statement that a later date should be used, count from the later date.

FDA also agrees that an exclusive patent licensee's interests may differ from those of the patent owner. Therefore, FDA has revised §§ 314.52(f) and 314.95(f) to start the 45-day period on the day following the date of receipt of the notice by the patent owner or its representative and by the approved application holder.

H. Section 314.101—Filing an Application and an Abbreviated Antibiotic Application and Receiving an Abbreviated New Drug Application (21 CFR 314.101)

63. The agency, on its own initiative, is revising § 314.101(e) to add a new paragraph stating that the agency will refuse to file a 505(b)(2) application or receive an ANDA if the drug product that is the subject of the 505(b)(2) application or ANDA is protected by a 5-year exclusivity period under section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act. This amendment is consistent with the statutory language and § 314.108(b)(2).

I. Section 314.107—Effective Date of Approval of a 505(b)(2) Application or Abbreviated New Drug Application Under Section 505(j) of the Act)

Proposed § 314.107 was intended to codify the requirements under section 505(c)(3) and (j)(4) of the act regarding the effective dates of approval for a 505(b)(2) application or an ANDA. For example, if the 505(b)(2) applicant or ANDA applicant certified that there are no relevant patents, that patent information has not been submitted, that the patent has expired, or that the patent is invalid, unenforceable, or not infringed, and the patent owner has not brought suit for patent infringement, proposed § 314.107(b)(1) would treat the date FDA issues an approval letter as the effective date of approval. If the 505(b)(2) applicant or ANDA applicant certified that the patent would expire on

a specific date, proposed § 314.107(b)(2) would treat that specific date as the effective date of approval. Proposed § 314.107(b)(3) described several situations in which the effective date of approval could vary, depending upon the disposition of patent litigation.

Proposed § 314.107 also implemented the "180-day exclusivity period" described in section 505(j)(4)(B)(iv) of the act. In brief, section 505(j)(4)(B)(iv) of the act states that if an ANDA contains a paragraph IV patent certification (declaring the patent to be invalid or not infringed) and the ANDA is for a drug for which a previous ANDA containing a paragraph IV patent certification has been submitted, approval of the subsequently submitted ANDA will be made effective 180 days after the date FDA receives from the previous ANDA applicant notice of the first commercial marketing of the drug or the date a court holds the patent that is the subject of the patent certification to be invalid or not infringed, whichever date is earlier (see section 505(j)(4)(B)(iv) of the act). Proposed § 314.107(c) provided that an applicant must be the first ANDA applicant to submit a substantially complete application with a paragraph IV certification and must have been sued for patent infringement in order to qualify for 180-day exclusivity.

64. One comment asked FDA to permit any person to contact FDA informally to determine whether the listed patent information was correct and later petition the agency to correct any errors. As proposed, § 314.107 did not provide for inquiries concerning patent information.

Sections 314.53(f) and 314.94(a)(12)(vii) describe the procedures that an applicant can use to question the validity of patent information. In brief, if an applicant disputes the accuracy or relevance of patent information, it should first notify FDA in writing and state the reasons for the disagreement. FDA will then request that the relevant NDA holder confirm the validity of the patent information, but will not change the patent information itself unless the NDA holder withdraws or amends the patent information. The agency believes that these procedures for determining the validity of patent information are sufficient, and, therefore, declines to adopt the change suggested by the comment.

65. FDA, on its own initiative, has amended § 314.107(b)(1) to state that an approval will become effective on the date FDA issues an approval letter except as provided under paragraphs (b)(3), pertaining to approvals resulting from the disposition of patent litigation; (b)(4), pertaining to approvals where an applicant has submitted multiple certifications; and (c), regarding subsequent ANDA submissions. These changes are to clarify that there are other situations that may make an approval effective.

66. Two comments would revise proposed § 314.107(b)(1)(iv) regarding a certification that a patent is "invalid or will not be infringed." The comments would have this certification state that the patent is "invalid and will not be infringed."

FDA declines to adopt the suggested language. The provision simply paraphrases the statutory language for a paragraph IV certification (see section 505(j)(2)(A)(vii)(IV) of the act). The agency has, however, amended the provision to account for a certification that a patent is unenforceable and, as stated earlier, removed the language regarding consent from the patent holder.

67. One comment asked FDA to amend proposed § 314.107(b)(1)(iv)(B)(*2*) to require NDA holders to have a role in or consent to licensing agreements between patent owners and ANDA applicants. The proposed rule would consider the effective date of approval for a 505(b)(2) application or an ANDA to be the date FDA issues an approval letter if, among other things, the drug product is covered by a patent licensing agreement and the 505(b)(2) application or ANDA contains a statement that the applicant has been granted a patent license and a statement from the patent owner that it has a licensing agreement with the applicant for the proposed drug product and that the patent owner consents to an immediate effective date.

As stated elsewhere in this final rule, FDA believes that the negotiations surrounding licensing agreements and the parties entering into such agreements are outside the scope of this rule. Additionally, as stated in the response to comment 43 above, the agency has deleted the provisions in § 314.107(b)(1)(iv) relating to consent by a patent owner to an immediate effective date of approval for a licensee.

68. The agency, on its own initiative, has made minor grammatical changes and other revisions to § 314.107 (b)(2) and (b)(3). These revisions replace "Upon patent expiration" with "Patent Expiration" and "Upon disposition of patent litigation" with "Disposition of patent litigation." Additionally, the changes specify that the patent owner must receive the notice of certification and clarify, in § 314.107(b)(3)(i)(B), the effective date of approval.

69. Proposed § 314.107(b)(3) described the effective date of approval of a 505(b)(2) application or ANDA upon disposition of patent litigation. Under proposed § 314.107(b)(3)(i)(A), if an applicant certified that the relevant patent was invalid or would not be infringed, and the patent owner or its representative brought suit for patent infringement, the effective date of approval for the 505(b)(2) application or ANDA would be 30 months after the date of receipt of the notice of certification of patent invalidity or noninfringement by the patent owner or its representative unless a court extended or reduced the 30-month period. Proposed § 314.107(b)(3)(i)(B) described the effective date of approval of a 505(b)(2) application or an ANDA upon disposition of patent litigation when the patented drug product also qualified for 5 years of market exclusivity. Proposed § 314.107(b)(3)(ii) through (b)(3)(iv) represented additional modifications to the effective date of approval due to court decisions or orders.

One comment concerned the proposed language in § 314.107(b)(3)(i) regarding the 30-month period. The comment would amend this provision to shorten or lengthen the 30-month period pursuant to a court order.

The suggested change is unnecessary because § 314.107(b)(3)(i) through (b)(3)(iv) explains how the 30-month period may be changed due to court decisions or orders.

The agency also emphasizes that disposition of patent litigation will not result in automatic approval of a pending application. FDA notes that section 505(c)(3)(C) and (j)(4)(B)(iii) of the act describe when approval of a 505(b)(2) application or an ANDA shall be made effective if an applicant submitting a 505(b)(2) application or ANDA has made a paragraph IV certification and has or has not been sued for patent infringement. For example, if the applicant made a paragraph IV certification, was sued for patent infringement, and the court hearing the patent infringement suit decided that the patent was either invalid or not infringed, section 505(c)(3)(C)(i) and (j)(4)(B)(iii)(I) of the act state, respectively, that approval of the 505(b)(2) application or ANDA may "be made effective on the date of the court decision." However, the agency interprets these provisions of the act as requiring, as a preliminary matter, final agency approval of the application in order for any approval to be made effective. Thus, an applicant with a tentative approval may not begin marketing its drug product until it has

received an approval letter from the agency because a tentative approval letter does not constitute a final "approval" of the application. In such cases, the agency will examine the application to determine whether there have been any changes in the conditions under which the application was tentatively approved. The tentative approval would become final and, therefore, effective only when the agency sends an approval letter to the applicant.

Similarly, an applicant that has not yet received a tentative approval letter may not begin marketing its drug product in the event that a court reaches a decision in any related patent infringement litigation because there is no final "approval" by FDA that could be made "effective" within section 505(c)(3)(C)(i) or (j)(4)(B)(iii) of the act.

Other provisions of the act support this interpretation of section 505(c)(3)(C)(i) and 505(j)(4)(B)(iii) of the act as they relate to the expiration of the 30-month period or the date of the court decision. For example, section 505(j)(3) of the act states that the agency shall approve an ANDA unless certain circumstances are found to exist. Section 505(j)(3)((A) of the act prevents the agency from approving an ANDA if the agency finds that "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity." Consequently, until FDA assesses the available information, often from an additional current good manufacturing practices inspection, it cannot determine whether the applicant's methods and controls used for the manufacture, processing, and packing of the drug are adequate to assure and preserve the drug's identity, strength, quality, and purity and therefore, under section 505(j)(3) of the act, whether the ANDA should be approved. Thus, unless FDA has formally approved an ANDA under section 505(j)(3) of the act, there is no "approval" that could be made effective under section 505(j)(4)(B) of the act upon resolution of the patent litigation. (Section 505(d) of the act establishes an analogous approval requirement for 505(b)(2) applications.)

The legislative history provides additional support for FDA's interpretation. In describing the provisions regarding effective dates of approval and court decisions, the House Report states:

> The Committee wishes to emphasize that the court *may not order an ANDA approved* under this provision. These are times when approval of an ANDA may be made effective *if the FDA has approved the ANDA.*

See H. Rept. 857, 98th Cong., 2d sess., Part 1, 27–28 (1984) (emphasis added). The same concept is applicable to 505(b)(2) applications (see id. at 34).

This interpretation of section 505(j)(4)(B) of the act reflects current FDA practice and revises the agency's previous policy that was stated in the preamble to the proposed rule (see 54 FR 28872 at 28894). It also clarifies the agency's position on delayed effective dates of approvals as expressed in the preamble to the final rule on ANDA content and format that was published in the **Federal Register** on April 28, 1992 (57 FR 17950 at 17956). Consequently, FDA, on its own initiative, has amended § 314.107(b)(3) to clarify when approval of an application may become effective and by adding a new paragraph (b)(3)(v) to state that, in order for an approval to become effective under paragraph (b)(3), the applicant must first receive a final approval letter from the agency.

70. One comment would restrict proposed § 314.107(b)(3)(ii) to district court orders. The comment would revise the rule to state: "If before the expiration of the 30-month period, or 7½ years where applicable, the district court decides such patent is invalid or not infringed, the approval will be made effective on the date of the district court order or judgment." The comment would also replace the words "a final order" in proposed § 314.107(b)(3)(iii) and (b)(3)(iv) with "an order or judgment."

FDA declines to limit the rule to district court orders. As stated in the preamble to the proposed rule, FDA interprets the requirement of a "court decision" to mean "a final decision of a court from which no appeal can or has been taken" (see 54 FR 28872 at 28895). Beginning the 180-day exclusivity period before the resolution of the appeals process would render the exclusivity valueless to a prudent applicant who delayed marketing until the issues were resolved on appeal.

FDA has, however, revised § 314.107(b)(3)(iii) and (b)(3)(iv) to refer to an "order or judgment" because both terms are sometimes used to refer to actions that terminate an action or decide a matter in litigation.

71. Proposed § 314.107(b)(4) concerned applicants who made multiple patent certifications. In essence, the proposed provision would consider the approval of a 505(b)(2) application or an ANDA to be effective on the last applicable date. One comment would amend proposed § 314.107(b)(4) by adding a new sentence stating:

> If the applicant has submitted certifications under § 314.50(i) or § 314.94(a)(12) and has submitted notice to the owner of the patent pursuant to § 314.95, and FDA subsequently receives a stipulation or order by the district court notifying it that the applicant has amended its answer to add new arguments, not included in that notice, in any ensuing suit for patent infringement, the date of approval will be calculated based on a 30-month period starting at the date of receipt by FDA of each such stipulation or order, and the approval will become effective on the last applicable date.

Alternatively, the comment suggested that an ANDA applicant who amended its answer to a patent infringement suit to include arguments that were not in the notice to the patent owner under § 314.95 would be considered to have been uncooperative in expediting the lawsuit. The comment explained that these revisions would prevent generic drug companies from amending their answers during patent infringement litigation to delay completion of a trial and also delay the start of the 30-month period.

FDA declines to adopt the comment's suggestion. As stated above, FDA has revised the notice requirements in §§ 314.52(c) and 314.95(c) to parallel the statutory language rather than specify notice requirements. The agency has neither the resources nor the expertise to engage in patent disputes or questions regarding sufficiency of notice. The statute leaves the issue of extending the 30-month period (based on a lack of cooperation between the parties in patent litigation) to the discretion of the trial court. The agency believes that the trial court should make determinations of cooperation on a case-by-case basis. Accordingly, the agency declines to amend the rule to consider an applicant to be uncooperative and to extend the 30-month period if the applicant amends an answer to a complaint in patent litigation to include an argument not reflected in the notice to the patent holder.

72. FDA received several comments on proposed § 314.107(c) and the 180-day exclusivity period against subsequent ANDA's. As proposed, § 314.107(c) would provide 180-day exclusivity to the first ANDA applicant that made a paragraph IV patent certification (that the patent was invalid or not infringed) and was sued for patent infringement. Seven comments said the language requiring an ANDA applicant to have been sued in order for the 180-day exclusivity period to become effective was contrary to the statute and to a judicial ruling in the

U.S. District Court for the District of Columbia.

Section 505(j)(4)(B)(iv) of the act can be applied straightforwardly only when an applicant who seeks the 180-day period of exclusive marketing has been involved in a patent infringement lawsuit. To apply the section where there has been no lawsuit would require that the agency ignore the textual relationship between section 505(j)(4)(B)(iii) and (j)(4)(B)(iv) of the act and assume that Congress intended, contrary to the goals it stated in the legislative history, to create an incentive for delay in generic competition, without any countervailing benefit to society. Moreover, it would provide a windfall to an applicant who has not devoted the considerable time and money necessary for patent litigation. Thus, consistent with the agency's longstanding interpretation of the act, § 314.107(c) applies only when the first applicant has been sued. Although, as the comments state, one Federal district court reached a contrary conclusion, the agency appealed that decision and, on appeal, the decision was vacated as moot (*Inwood Laboratories, Inc.* v. *Young*, 723 F.Supp. 1523 (D.D.C. 1989), *vacated as moot*, no. 89–5209 (D.C. Cir., November 13, 1989). The agency has not altered its interpretation of the act.

FDA has, however, revised § 314.107(c) to clarify other issues, such as the start and end of the 180-day exclusivity period, and to make minor editorial changes.

73. One comment suggested revising proposed § 314.107(c) to state that the 180-day exclusivity period does not apply to delay the effective date of approval of licensees to the NDA holder.

As stated above, FDA does not believe that an ANDA applicant who has made a paragraph IV certification and obtained a patent license should be able to circumvent a 180-day exclusivity period. Consequently, the agency declines to amend the provision as requested by the comment.

74. Two comments would revise proposed § 314.107(c) to extend the 45-day period in which patent owners have to file suit against an ANDA applicant. The proposal referred to the statutory 45-day period in which a patent owner would have to file suit against an ANDA applicant. The comments would extend the 45-day period upon request or when the ANDA applicant and the patent owner agree to an extension.

FDA declines to accept the comments' suggestion. The 45-day period for filing a lawsuit against an ANDA applicant is fully consistent with section 505(j)(4)(B)(iii) of the act, and the agency finds that there are sound policy reasons that outweigh extensions of the 45-day period. For example, if an ANDA applicant has provided notice to a patent owner stating that the ANDA applicant believes that the patent is invalid or would not be infringed (a paragraph IV certification), the patent owner may elect to bring suit against the ANDA applicant for patent infringement. If the suit is brought within 45 days from the date the ANDA applicant provided the notice, section 505(j)(4)(B)(iii) of the act precludes the agency from granting a final approval of the ANDA. If suit is not brought within 45 days, FDA could grant a final approval of the ANDA upon expiration of this time period, assuming that the ANDA met all applicable requirements for approval. Thus, amending the rule to provide the patent owner an extension to file suit beyond the 45-day period would not prevent the agency from approving ANDA's during the extension (because the statutory restriction against making an approval effective would no longer apply), even if the patent owner later decided to bring suit against the ANDA applicant and prevailed in that lawsuit. Such a result would waste agency and industry resources.

FDA also notes that, in situations where an ANDA applicant has amended its notification to the patent owner and approved NDA holder to make it more complete, the agency may, under § 314.95(f), consider the 45-day period to begin on the day after the date of receipt of the amended notification.

75. One comment would revise proposed § 314.107(c) to begin the 180-day exclusivity period "on the first day that a court would allow non-infringing marketing (unless that decision were stayed)" or "30 months from receipt of notice."

The agency declines to revise the rule as suggested. The rule, which paraphrases the statutory language at section 505(j)(4)(B)(iv) of the act, better reflects the plain meaning of the act. Revising the rule as requested by the comment would begin the 180-day exclusivity period at the end of the 30-month period without regard to whether the applicant had commenced marketing on that date.

76. Proposed § 314.107(c)(1)(i) would provide 180-day exclusivity to the first ANDA applicant to submit a complete ANDA with a paragraph IV patent certification and "to be sued within 45 days of the patent owner's receipt of notice." One comment said the rule, as drafted, created an incentive for frivolous claims of patent invalidity or noninfringement because it would give ANDA applicants exclusivity even if the applicant was unsuccessful in defending against the patent owner's lawsuit. The comment would replace the phrase "to be sued within 45 days" with "and to successfully defend a suit brought within 45 days."

FDA agrees and has amended § 314.107(c) accordingly.

77. FDA received several comments regarding proposed § 314.107(c)(1)(i) and (c)(1)(ii). These provisions concerned the start of the 180-day exclusivity period. Proposed § 314.107(c)(1)(i) would begin the 180-day exclusivity period on the date of the first commercial marketing of the drug product by the first ANDA applicant who submitted a substantially complete ANDA containing a certification that the patent was invalid or not infringed and who was sued for patent infringement within 45 days after providing notice to the patent owner. Alternatively, proposed § 314.107(c)(1)(ii) would begin the 180-day exclusivity period on the "date a decision of the court holding the relevant patent invalid or not infringed" if that date was earlier than the date of the first commercial marketing. One comment would revise proposed § 314.107(c)(1)(ii) to include a cross-reference to the language in § 314.107(b)(3) on patent litigation.

FDA declines to adopt the suggested revision. The agency believes that the meaning of § 314.107(c)(1)(ii) is sufficiently clear so that the court referred to in § 314.107(c)(1)(ii) is the court deciding the patent infringement suit. However, for reasons stated elsewhere in this document, the agency has amended this provision to include a reference to unenforceable patents.

78. One comment would amend § 314.107(c), (c)(1)(i), and (c)(1)(ii) to permit an ANDA applicant to decide whether to start the 180-day exclusivity period on the date it notifies the agency that the applicant has begun commercial marketing of the drug product or to wait to see whether the court decision is appealed. If an appeal did result, the comment would permit the ANDA applicant to have the 180-day period begin when a court issues a decision on the appeal.

FDA declines to amend the provision as suggested by the comment. The provision is consistent with section 505(j)(4)(B)(iv) of the act by beginning the 180-day period on the date the first ANDA applicant has notified the agency that it has begun commercial marketing of the drug product or the date of a court decision holding the patent to be invalid or not infringed, "whichever is earlier" (see section 505(j)(4)(B)(iv) of the act.) Allowing an applicant to begin marketing before the commencement of the 180-day exclusivity period would,

in effect, extend the exclusivity period in a manner that is inconsistent with the plain meaning of the act. FDA also notes that the court decision must be a final decision from which no appeal can be or has been taken (see 54 FR 28872 at 28895).

79. FDA received four comments regarding "substantially complete" applications under proposed § 314.107(c)(2). Proposed § 314.107(c)(2) would consider an ANDA to have been "previously submitted" with respect to another application for the same listed drug "if the date on which the first application was both substantially complete and contained a certification that the patent was invalid or not infringed is earlier than the date on which the second application was both substantially complete and contained the same certification." The proposal also stated that a "substantially complete" application "must contain the results of any required bioequivalence studies, or, if applicable, a request for a waiver of such studies."

One comment asked FDA to provide information as to which ANDA was the first "substantially complete" ANDA. The comment suggested that disclosing such information did not present any confidentiality problems because the ANDA applicant would have revealed the existence of the ANDA when it provided notice of certification of invalidity or noninfringement of the patent to the patent owner and NDA holder.

FDA agrees, in part, with the comment. Disclosing whether an ANDA had been received for a specific listed drug would enable manufacturers to decide whether to develop a generic version of that drug and perhaps conserve the manufacturer's resources. Such knowledge could, in turn, effectively reduce the number of applications for the same product and thus also conserve agency resources. The agency, therefore, will disclose whether an ANDA has been received for a particular drug, but, in order to preserve the confidentiality of the applicant, will not disclose when the application had been received or the applicant's identity. Potential applicants who wish to inquire whether an ANDA for a specific drug has been received can contact the Regulatory Support Branch (HFD–615), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–0315.

80. Two comments disagreed with the language regarding "substantially complete" applications. One comment said FDA should only determine whether an ANDA contains a bioequivalence test or waiver request and not focus on the results of any required bioequivalence studies. The second comment suggested that a "substantially complete" ANDA be one that contained a paragraph IV patent certification and a bioequivalence study that is ultimately approved. The comment said this change would deter ANDA applicants from submitting "superficial" bioequivalence tests. The comment also suggested that the agency establish criteria as to whether changes to an ANDA were so substantial that the ANDA could no longer be considered as the first to be filed.

Since publication of the proposed rule, FDA has clarified its policies regarding the submission of incomplete ANDA's. Under the earlier policy, ANDA applicants could submit ANDA's with bioequivalence study protocols and could provide bioequivalence study data at a later date. This policy resulted in a significant and unwarranted expenditure of resources in reviewing applications that had little potential for approval. Thus, in the Federal Register of April 28, 1992, FDA announced that it would no longer accept an ANDA that does not contain complete bioequivalence study data if such data are required for approval (see 57 FR 17950 at 17959). A "substantially complete" application, therefore, should have a complete bioequivalence study, or other information to show bioequivalence that could support approval of the application. FDA will examine the bioequivalence information upon submission and, if the agency determines that the bioequivalence information is facially insufficient to support a finding of bioequivalence, the agency will not review the application under § 314.101(d). A decision by the agency after receipt of an application that the bioequivalence information is inadequate for approval does not necessarily mean that the application was not substantially complete at the time of submission.

FDA also declines to establish criteria to establish whether changes to an ANDA were so substantial that it could not be considered to have been filed. While certain changes in an ANDA (e.g., a change in the listed drug) would amount to a new filing for purposes of § 314.107(c)(2), other changes (e.g., minor labeling changes) would not. The agency believes a case-by-case approach is preferable because many products and manufacturers may be unique.

81. The agency, on its own initiative, has revised the provisions in § 314.107 (c)(2) and (c)(3) to clarify their intent. These provisions address the issues of the "applicant submitting the first application" for exclusivity purposes, what constitutes a "substantially complete" application, and the effective dates of approval for subsequently submitted applications if the first applicant is not "actively pursuing" approval. FDA has made similar editorial changes at § 314.107(c)(4).

82. Four comments addressed proposed § 314.107(c)(3). The proposed provision would make an ANDA that had been received after FDA had already received an ANDA for the same drug immediately effective if the agency concluded that the first ANDA applicant "is not actively pursuing approval of its abbreviated application." Three comments asked FDA to define the phrase "actively pursuing approval."

For purposes of this rule, the phrase "actively pursuing approval" is intended to encompass a drug sponsor's good faith effort to pursue marketing approval in a timely manner. In determining whether a sponsor is actively pursuing marketing approval, FDA will consider all relevant factors, such as the sponsor's compliance with regulations and the timeliness of its responses to FDA's questions or application deficiencies during the review period.

83. One comment would revise proposed § 314.107(c)(3) to make a subsequently received ANDA immediately effective upon a finding that the first applicant is not actively pursuing approval "if [the subsequent application is] otherwise eligible for an immediately effective approval."

The agency agrees and has amended the provision accordingly. This change will remind applicants that FDA will make approval of a subsequent abbreviated application immediately effective if it satisfies all applicable requirements and FDA has concluded that the first applicant is not actively pursuing approval of its abbreviated application.

84. FDA received five comments regarding the interpretation of "the court" and court judgments in proposed § 314.107(e)(1). Proposed § 314.107(e)(1) stated that "the court" in § 314.107(b) and (c) referred to "the court that enters final judgment from which no appeal can be or has been taken." Three comments supported the proposal, but two comments argued that FDA had misconstrued the 1984 amendments. One comment argued that the court finding a patent to be invalid or not infringed should be "the court of first instance" or district court because a decision that a patent was invalid or not infringed or a decision to issue an injunction would be done by a district court. Another comment argued that interpreting "the court" to mean the

court that enters final judgment "effectively gives a patent owner an additional extension of the patent * * * for the duration of the appeal" and delay generic competition. The comment would revise the rule to permit an ANDA applicant to market its drug product after it had prevailed at the trial court level.

FDA declines to amend § 314.107(e)(1) as suggested by the comments. To construe "the court" as a district court, regardless of any appeal of the district court decision, would deny the benefits of exclusivity to a prudent applicant that delayed marketing its product until resolution of an appeal by the patent holder (see 54 FR 28872 at 28894). Moreover, if the patent holder appealed the district court decision and were able to obtain a stay or an injunction against the marketing of the applicant's product, the applicant could lose the entire 180-day exclusivity period before the stay or injunction were lifted.

Given these considerations, FDA believes that any reference to "the court" must be the court that enters final judgment from which no appeal can be or has been taken. (The reference to "appeals" does not include the certiorari process. The likelihood of an appellate court decision being heard and overruled by the Supreme Court is too remote to warrant delaying marketing and exclusivity pending resolution of a petition for writ of certiorari.) This interpretation avoids potentially premature decisions on the effective date of ANDA approval and the loss of 180-day exclusivity. FDA has, however, also revised § 314.107(e)(2) to clarify which court decisions will represent the "final" judgment.

85. One comment would revise proposed § 314.107(e)(2) to refer to a court order or judgment rather than simply a court judgment.

As amended, § 314.107(e)(2) refers to a court "decision," which could be in the form of either an order or a judgment. The agency has also made minor changes to § 314.107(e)(2) to clarify that the court decisions involve patent issues and that a higher court can hold or affirm a lower court decision that a patent is invalid, unenforceable, or not infringed.

86. A second comment would revise proposed § 314.107(e)(2) to require applicants to submit copies of a court order or judgment to the Division of Generic Drugs or "New Drug Evaluation Division (where applicable)."

FDA agrees with the comment, and has added § 314.107(e)(2)(iv) to require applicants to send a copy of a final decision to the Office of Generic Drugs, or to the appropriate division in the Office of Drug Evaluation I or the Office of Drug Evaluation II, whichever is applicable.

87. Proposed § 314.107(f) described how the 45-day period for filing a patent infringement suit would be determined. In brief, under proposed § 314.107(f)(1), the 45-day period would begin on the day after the date the patent owner or approved application holder, if an exclusive patent licensee, received a notice of certification of invalidity or noninfringement of the patent. Proposed § 314.107(f)(2) would require the 505(b)(2) applicant or ANDA applicant to notify FDA whether an action for patent infringement had been filed. Several comments objected to language in proposed § 314.107(f) that would consider notice to or actions by exclusive licensees to be equivalent to notice to or actions by a patent owner. The comments said that exclusive licensees do not always share the patent owner's interests.

FDA agrees and has revised the rule to remove language that would consider exclusive licensees to be equivalent to patent owners.

88. One comment objected to proposed § 314.107(f)(1) because it would start the 45-day period on the day after the date the patent owner or the approved application holder, if an exclusive patent licensee, received notice of invalidity or noninfringement of a patent. The comment argued that the 45-day period should begin on the day after the date that the patent owner and the approved application holder received notice and, if these dates differed, the latest date should mark the start of the 45-day period.

The agency agrees with the comment and has revised § 314.107(f)(1) to begin the 45-day period on the day after the date the patent owner and the approved application holder have received the applicant's notice of certification of invalidity or noninfringement of a patent.

89. FDA received several comments on proposed § 314.107(f)(2). Absent a notice of an action for patent infringement, the proposal would make the approval of an ANDA or 505(b)(2) application effective immediately upon the expiration of the 45-day period for filing a patent infringement suit or upon FDA's completion of the review and approval process, whichever is later. The comments noted that the regulation would have ANDA or 505(b)(2) applicants notify FDA whether a patent infringement suit had been filed and asked FDA to permit, by regulation, patent owners to notify FDA whether it had brought suit. Alternatively, some comments would require the ANDA or 505(b)(2) applicant certify that it had not been sued. The comments explained that these changes were necessary because ANDA and 505(b)(2) applicants would have no interest in notifying FDA whether suit had been filed because, without such notice, they could immediately secure effective approval of an application.

The agency has amended § 314.107(f)(2) to permit patent owners or their representatives to notify FDA whether a patent infringement suit has been filed. The statute does not require applicants to certify that they have not been sued, and the agency does not believe such a burden to be necessary.

The agency has also made minor revisions to § 314.107(f)(2) to place more emphasis on an applicant's obligation to notify FDA immediately of the filing of any legal action within 45 days of receipt of a notice of certification.

Additionally, the agency has made a grammatical change in § 314.107(f)(2) to clarify that applicants must send the notification to the Office of Generic Drugs or to the appropriate division in the Center for Drug Evaluation and Research reviewing the application.

90. One comment addressed the requirement in proposed § 314.107(f)(2) that a 505(b)(2) applicant or ANDA applicant notify FDA whether an action for patent infringement had been filed "before the expiration of the 45-day time period or the completion of the agency's review of the application, whichever occurs later." The comment argued that a patent owner had 45 days to file a lawsuit after receiving a notice of certification of invalidity or noninfringement of a patent and, therefore, a party should have an additional time period beyond the 45-day period for filing an action for patent infringement for notifying the agency whether an action had been filed. The comment would revise the rule to give a party an additional 15 days beyond the 45-day period to notify FDA whether an action for patent infringement had been filed.

The agency declines to revise the rule as suggested. FDA believes it is important to learn immediately if an action for patent infringement is filed before the completion of the 45-day period to avoid an erroneous approval with an immediate effective date.

FDA has, therefore, amended § 314.107(f)(2) to require applicants to notify FDA immediately whether any legal action has been filed. The agency has also amended this subsection to clarify the identity of the "applicant."

91. FDA has, on its own initiative, clarified its notification requirements in

§ 314.107(f)(2)(iii). As proposed, § 314.107(f)(2)(iii) would have required parties to identify a drug by its established name, but would not have expressly required any identification of the drug if no established name existed. The agency has amended this provision to require identification of the drug product by its established name or, if no established name exists, its active ingredient(s).

92. One comment asked FDA to publish information regarding the status and progress of patent infringement suits so other ANDA applicants could decide whether to intervene in the suit "and ask that the 30-month period be shortened or lengthened in the event that it feels that one or both of the litigants are not reasonably cooperating in expediting the action." Alternatively, the comment asked FDA to permit any interested party to petition the agency "to remove an ANDA from exclusivity considerations if it has not proceeded with due diligence—either in prosecution of its ANDA or defense of an infringement suit."

FDA believes that ANDA applicants are capable of monitoring the progress of patent litigation without imposing the additional burden of acquiring and publishing information on patent litigation on FDA. The agency, therefore, declines to adopt the comment.

FDA also declines to amend the rule to permit third parties to petition the agency to deny exclusivity to an ANDA due to the ANDA applicant's actions during litigation. Under the statute, the reduction or enlargement of the 30-month period is left to the trial court's discretion. Intervention by the agency is unwarranted.

93. One comment suggested replacing the words, "action to defend," in proposed § 314.107(f)(2)(iv) with the words, "action for patent infringement." The comment said that "action to defend" was not a term of art.

FDA agrees and has adopted the comment.

94. FDA, on its own initiative, has modified the language regarding waivers in § 314.107(f)(3). The change is intended to clarify that the patent owner does not object to FDA's approval of an ANDA or 505(b)(2) application with an immediate effective date and to account for those situations where the ANDA applicant or 505(b)(2) applicant and the patent owner have agreed to extend the 45-day period.

J. Section 314.108—New Drug Product Exclusivity

Proposed § 314.108 was intended to implement the new drug exclusivity provisions under section 505(c)(3)(D) and (j)(4)(D) of the act. This section of the act provides specific time periods, known as new drug product exclusivity or market exclusivity, during which the effective date of approval for a 505(b)(2) application or an ANDA must be delayed or, in some cases, a 505(b)(2) application or an ANDA cannot be submitted. For example, section 505(c)(3)(D)(i) and (j)(4)(D)(i) of the act grant a 10-year period of exclusivity to new chemical entities that were approved during January 1, 1982, to September 24, 1984. Section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act grant a 5-year period of exclusivity to new chemical entities approved after September 24, 1984. These sections of the act expressly state that no 505(b)(2) application or ANDA may be submitted during the exclusivity period except that such applications may be submitted after 4 years if they contain a certification of patent invalidity or noninfringement. Section 505(c)(3)(D)(iii), (c)(3)(D)(iv), (j)(4)(D)(iii), and (j)(4)(D)(iv) of the act grant a 3-year period of exclusivity to an application or supplemental application that is approved after September 24, 1984, and contains "reports of new clinical investigations (other than bioavailability studies) essential to the approval" of the application or supplemental application and "conducted or sponsored by" the person submitting the application or supplemental application.

Section 505(c)(3)(D)(v) and (j)(4)(D)(v) of the act granted a 2-year period of exclusivity to drugs that are not chemical entities or for certain changes to already approved products that were approved during January 1, 1982, to September 24, 1984. FDA did not propose any regulations for this 2-year period because it expired on September 24, 1986.

The exclusivity provisions of the act do not provide any protection from the marketing of a generic version of the same drug product if the generic version is the subject of a full NDA submitted under section 505(b)(1) of the act.

95. Proposed § 314.108(b)(4) would provide 3 years of exclusivity to an application that was submitted under section 505(b) of the act, was approved after September 24, 1984, was for a drug product containing an active moiety that had been previously approved in another application under section 505(b) of the act, and contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application. Proposed § 314.108(b)(5) would provide 3 years of exclusivity to a supplemental application that was approved after September 24, 1984, and contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application.

Several comments addressed the scope of new drug exclusivity. Two comments said FDA should grant exclusivity for any change to an approved drug product or, alternatively, should grant exclusivity based on specific types of studies, such as studies intended to reduce drug dosing or drug efficacy study implementation (DESI) upgrade studies. One comment disagreed with the preamble to the proposed rule, which stated, "FDA expects that only those changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use would be granted exclusivity" (54 FR 28872 at 28899). Two comments asked FDA to clarify whether a clinical investigation establishing new risks could be eligible for exclusivity. The preamble to the proposed rule had indicated that such studies would not qualify for exclusivity because "protection of the public health demands that all products' labeling contain all relevant warnings" (see 54 FR 28872 at 28899). One comment said FDA should accept an applicant's claim of exclusivity alone.

Two other comments sought to limit exclusivity or clarify its scope. One comment argued that the rule was too broad, would confer "an unearned windfall," and stifle generic competition. The comment explained that some variations, such as reductions in dosage, require little effort but would nevertheless qualify for exclusivity. The comment suggested that the rule define what types of changes would qualify for exclusivity. The second comment agreed with the preamble that DESI upgrades should not qualify for exclusivity but asked FDA to create a procedure whereby parties could contact FDA to determine whether exclusivity information was accurate. The comment said this would enable third parties to decide whether to challenge decisions to grant or deny exclusivity.

FDA disagrees with those comments that would grant exclusivity for any change to an approved drug product or accept, without question, an applicant's claim that it is entitled to exclusivity. Under the statute and this final rule, certain drugs or changes to drugs can receive 3 years of exclusivity if the application or supplement to an

application "contains reports of new clinical investigations (other than bioavailability studies) essential to the approval * * *" (see section 505(j)(4)(D)(iii) and (j)(4)(D)(iv) of the act). The phrase "essential to the approval" suggests that the clinical investigations that warrant exclusivity must be vital to the application or supplement. As stated in the preamble to the proposed rule, "to qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective" (see 54 FR 28872 at 28900). For example, the agency would not consider studies to support a switch from prescription to over-the-counter (OTC) status to be "essential to approval" if the agency already had sufficient information to conclude that the OTC product would be safe and effective. (In OTC switch situations, FDA encourages applicants to consult FDA to determine whether clinical investigations or any other actions are necessary to permit FDA to approve a switch in a product's status.)

FDA declines to define in the regulation the kinds of supplemental applications that, if supported by clinical investigations, would warrant 3-year exclusivity. Although the preamble to the proposed rule identified certain types of changes in a product that would normally warrant exclusivity (changes in active ingredient, strength, dosage form, route of administration, or conditions of use), the agency did not intend to suggest that other types of changes would not qualify. For example, changes in dosing regimen have resulted in grants of 3-year exclusivity. Changes that would not warrant exclusivity are, as discussed in the preamble to the proposed rule, changes in labeling that involve warnings or other similar risk information that must be included in the labeling of generic competitors. Applicants obtaining approval for such changes in labeling would, in any event, have no valid interest in precluding such information from the labeling of other products. Furthermore, FDA does not consider a study to be "essential to approval" simply because the applicant conducted it and submitted the study for agency review (Ref. 1).

FDA's interpretation is supported by statements that were made during the congressional debates surrounding the 3-year exclusivity provisions. Senator Orrin Hatch described the 3-year exclusivity provisions upon approval of certain supplemental applications as protecting "some changes in strength, indications, and so forth, which require considerable time and expense in FDA required clinical testing" (130 Congressional Record S10505, August 10, 1984) (statement of Senator Hatch)). Representative Henry Waxman said 3-year exclusivity was intended to "encourage drugmakers to obtain FDA approval for significant therapeutic uses of previously approved drugs" (130 Congressional Record H9114, (September 6, 1984)). Thus, an applicant is not entitled to 3-year exclusivity merely because it supplements an approved application based in part on a clinical investigation or because it certifies to FDA that the clinical investigation is essential to approval of the application or supplement.

FDA also declines to create a new procedure whereby a party could contact FDA to determine whether exclusivity information is accurate. Interested parties can obtain information on exclusivity decisions through the Freedom of Information Act process (21 CFR part 20). Parties who wish to challenge an exclusivity decision can utilize the citizen petition procedures (21 CFR 10.30).

96. One comment suggested that products whose labeling may not include certain therapeutic indications (due to exclusivity or patent protection) be listed in the Orange Book as not being therapeutically equivalent to the innovator product.

FDA addressed this comment in its response to a citizen petition submitted by the Pharmaceutical Manufacturers Association (PMA). The response stated, in pertinent part:

> In drafting the 1984 Amendments, the only mechanism that Congress provided for enforcing the exclusivity accorded a new indication is the requirement that ANDA's and 505(b)(2) applications be given delayed effective approval for the exclusive indication. During the period that ANDA's and 505(b)(2) applications may not be made effective, pioneers thus have the exclusive right to promote and label their products for the exclusive indication. Nothing in the language of the amended statute or its legislative history, however, suggests that Congress intended the granting of exclusivity for a new indication to alter therapeutic equivalence ratings. Moreover, it would be inconsistent with the established standards for making therapeutic equivalence determinations to rate two products as not therapeutically equivalent simply because one is labeled with fewer than all the approved indications.
>
> FDA's standards for therapeutic equivalence determinations * * * have always been based upon scientific considerations relevant to predicting the comparative pharmacological behavior of two products in or on the human body. There is no scientific basis for concluding that differences in recommended indications are relevant to this prediction. For example, the fact that a particular brand of drug is recommended in a medical journal article for an unlabeled use, does not, from a scientific standpoint, render other brands of the same drug therapeutically or biologically inequivalent. Similarly, the fact that a pioneer drug is labeled with a protected indication does not mean that generic copies of the same drug are not therapeutically equivalent to the pioneer.
>
> In absence of any suggestion in the statute or legislative history that Congress intended FDA to alter the scientific basis of therapeutic equivalence ratings to enforce exclusivity, FDA declines to consider non-scientific criteria, i.e., the existence of exclusive indications, in making therapeutic equivalence decisions.
>
> (Ref. 2)

FDA has not changed this position and, therefore, declines to adopt the comment.

97. Many comments objected to the definition of "active moiety" and the references to active moieties and new chemical entities throughout proposed § 314.108. The comments said the definitions lacked statutory support and were contrary to two court decisions, *Abbott Laboratories* v. *Young*, 691 F.Supp. 462 (D. D.C. 1988), *remanded*, 920 F.2d 984 (D.C. Cir. 1990), and *Glaxo Operations UK Ltd.* v. *Quigg*, 706 F.Supp. 1224 (E.D. Va. 1989), *aff'd*, 894 F.2d 392 (Fed. Cir. 1990). Two comments added that the definition of "active moiety" was also too restrictive because it excluded chelates, clathrates, and other noncovalent derivatives. The comments, in general, would delete all references to "active moiety" and "new chemical entity" and refer only to "active ingredients." Some comments would also define "active ingredient" as the active ingredient found in the finished dosage form before the drug is administered to the patient.

Subsequent to the close of the comment period, the interpretation of the act urged by the comments and adopted by the district court in *Abbott Laboratories* v. *Young* (providing 10 years of exclusivity under section 505(j)(4)(D)(i) of the act for products offering the same therapeutic moiety in different active ingredient forms if the salt or ester form was approved subsequent to the pure therapeutic moiety form) was rejected by the United States Court of Appeals for the District of Columbia. Noting that such an interpretation would award exclusivity to both an active moiety and a salt if the application containing the active moiety were submitted first, but would award exclusivity only to the salt if the salt

were submitted first, the court of appeals rejected the interpretation as "farfetched because it is not consistent with any legislative goal" (see *Abbott Laboratories* v. *Young*, 920 F.2d 984, 989).

Although the court of appeals appeared to agree with the agency's conclusion that exclusivity should be limited to the first approved product containing the active moiety, the court found the agency's parsing of the operative statutory phrase "active ingredient (including any salt or ester of the active ingredient)" to be linguistically impermissible as set forth in the agency's administrative decision denying 10-year exclusivity to Abbott. Rather than interpret the term "active ingredient" broadly to include the concept of active moiety, the agency interpreted the term narrowly to refer to the form of the moiety in the product, but interpreted the parenthetical phrase "(including any salt or ester of the active ingredient)" broadly to include all active ingredients that are different but contain the same active moiety. Although the court noted that the agency had, subsequent to the administrative decision, voiced the more linguistically permissible construction (interpreting the term "active ingredient" to refer to active moiety), the court found that it could not consider this construction because it was not relied upon in the administrative decision. The court thus remanded the case to the district court with instructions to remand the issue to the agency for further consideration.

The agency has concluded that the term "active ingredient," as used in the phrase "active ingredient (including any salt or ester of the active ingredient)," means active moiety. Thus, the agency declines to adopt the comments suggesting removal of the definition of, and references to, "active moiety" from § 314.108.

FDA disagrees with the assertion that the definition of "active moiety" should not exclude chelates, clathrates, and other noncovalent derivatives. As stated in the preamble to the proposed rule, exclusivity is intended to provide incentives for innovation (see 54 FR 28872 at 28898 and 28899). The addition of a chelate, clathrate, or other noncovalent derivative generally does not affect the active moiety of a drug product. The agency, therefore, does not believe that providing exclusivity for chelates, clathrates, and other noncovalent derivatives of a previously approved active moiety would be consistent with the statutory intent.

98. FDA received a number of comments regarding the term "substantial support" in the definition of "conducted or sponsored by the applicant" in proposed § 314.108(a). The proposed rule stated, "Ordinarily, substantial support will mean providing 50 percent or more of the cost of conducting the study" (see 54 FR 28872 at 28930). The comments said the 50 percent figure was unrealistic, unnecessary, or unauthorized by law and argued that cost should not be a controlling factor in determining new drug exclusivity. Other comments said the rule should permit firms to buy studies because there is no basis to grant exclusivity to a firm that purchases an NDA and to deny exclusivity to a firm that purchases a study. One comment asked how FDA would treat a publicly funded study.

The 50-percent contribution requirement reflects a reasonable interpretation of section 505 (j)(4)(D)(iii) and (j)(4)(D)(iv) of the act. A study can be conducted by or for only one applicant. Exclusivity based on less than 50-percent funding would allow multiple parties to claim exclusivity against ANDA applicants as well as each other. Moreover, the legislative history indicates that Congress created 3-year exclusivity to protect products whose development required a significant time commitment and "an investment of some magnitude" (see 130 Congressional Record S10504 (August 10, 1984) (statement of Senator Hatch); 130 Congressional Record H9124–H9125 (September 6, 1984) (statement of Representative Waxman)). Obviously, if a sponsor provided 50 percent or more funding to a study, its investment represents a substantial portion of the study's funding.

FDA acknowledges that there may be some rare circumstance in which less than 50-percent funding could constitute "substantial support" and merit exclusivity. FDA has, therefore, revised the rule to require: (1) A certified statement from a Certified Public Accountant that the applicant provided 50 percent or more of the cost of conducting the study; or (2) an explanation from the applicant why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent if the applicant did not sponsor the investigational new drug application. The agency has made a corresponding change to § 314.50(j)(4)(iii).

With regard to studies that the applicant has purchased and publicly funded studies, FDA agrees that an applicant who has purchased exclusive rights to a study should be able to obtain new drug exclusivity. FDA, therefore, has revised the definition of "conducted or sponsored by the applicant" to state that the purchase of nonexclusive rights to an investigation does not satisfy the definition. FDA emphasizes that the applicant must have exclusive rights to the purchased study in order to be deemed to have sponsored a study. The purchase of nonexclusive rights by different parties could result in multiple claims of exclusivity for the same study. For these reasons, FDA also believes that most, if not all, publicly funded studies will not qualify for exclusivity. These studies are usually publicly available, so FDA will not give one applicant exclusive rights based on a study that, by virtue of its funding, belongs to the general public and is publicly available.

99. The agency, on its own initiative, has amended the definition of "date of approval" to note that the date of approval "refers only to a final approval and not to a tentative approval that may become effective at a later date." This change reflects FDA's position that drug products with delayed effective dates of approval are not listed drugs and that an "approval with a delayed effective date is tentative and does not become final until the effective date" (see 57 FR 17950 at 17953).

100. One comment said proposed § 314.108(a) failed to correspond to proposed § 314.50(j)(4)(i), which states that § 314.108(a) defines "new" and "clinical investigations." Proposed § 314.50(j)(4)(i) contained an error. The proposed rule does not contain separate definitions for "new" and "clinical investigations"; it does, however, define "new clinical investigations" at § 314.108(a). FDA has corrected § 314.50(j)(4)(i) accordingly.

101. One comment objected to the last sentence in the definition of "new clinical investigation." The comment claimed that the definition would "unnecessarily, and contrary to the Statute, "expand and award an exclusivity for a previously submitted study; and it unjustifiably distinguishes between safety and effectiveness."

Under the statute, 3-year exclusivity is awarded if the application or supplemental application contained reports of new clinical investigations that were conducted or sponsored by the applicant and were essential to the approval of the application or supplemental application (see section 505(j)(4)(D)(iii) and (j)(4)(D)(iv) of the act). The legislative history indicates that 3-year exclusivity is for investigations requiring a considerable investment of time and money and that are necessary for approval of important innovations (see 54 FR 28872 at 28899).

Thus, FDA interprets "new clinical investigation" as a clinical investigation whose data have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug for any indication or safety in a new patient population and do not duplicate the results of another investigation relied upon by FDA to demonstrate a previously approved drug's effectiveness or safety in a new patient population. An applicant is not limited to recently conducted clinical investigations; a clinical investigation that provides a "new" basis for drug approval can qualify for exclusivity.

102. Two comments recommended revising the rule to address transfers of new drug exclusivity between an applicant and all predecessors in interest, including licensors, assignors, joint venture partners, or other parties.

New drug exclusivity is not a property right, but is rather a statutory obligation on the agency. This statutory obligation is based on data and information in an approved application. Although an applicant may purchase an application or rights to data and information in an application (i.e., exclusive rights to a new clinical investigation), from which exclusivity would flow, there is no property right to exclusivity itself that can be transferred separately and apart from the application or data upon which exclusivity is based. The agency does, however, permit the submission or approval of an ANDA when the holder of the exclusivity permits FDA to receive or approve the ANDA.

FDA notes that joint venture partners differ from licensees, assignors, etc., because joint venture partners share in developing a drug product. Consequently, FDA suggests that joint venture partners carefully consider how they will seek approval of an application and define their rights and interests in the application to avoid questions regarding applicability of the exclusivity provisions of the act.

As stated above, FDA has revised the definition of the phrase, "conducted or sponsored by the applicant," to construe a party who has purchased exclusive rights to a study to have "conducted or sponsored" the study. This change will enable a party who has acquired exclusive rights to a study to seek exclusivity.

103. Four comments asked FDA to create a mechanism that would determine whether a study was "essential for approval" either before an application would be submitted or before the study began. Proposed § 314.108(a) stated that "essential to approval" with regard to an investigation "means that the application could not be approved by FDA without that investigation, even with a delayed effective date." The proposal, however, did not discuss the procedure by which FDA would determine a study to be "essential to approval."

FDA declines to accept the comments. FDA cannot determine whether a study is essential for approval until the application is approved. Research goals and objectives often change during clinical investigations. For example, the results from a study designed to support a new indication could generate interest in a completely different indication. The product ultimately approved may be a different product from that characterized in the original application. It is also possible that newly available data in the public domain will obviate the need for the study prior to approval. Thus, FDA will decide whether a study is essential for approval at the time of approval.

The agency has, however, amended the definition of "essential to approval" to delete the reference to a delayed effective date. This change is necessary because the agency no longer regards an application with a delayed effective date as being approved. Instead, FDA considers such applications as being tentatively approved (see 57 FR 17950 at 17953).

104. Proposed § 314.108(b)(2) would provide 5 years of exclusivity for a new chemical entity if a drug product containing the new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act. One comment said FDA should deny 5-year exclusivity to any section "505(b)(2) application for a new chemical entity that relies upon one or more investigations that are essential for approval of the application but which were not conducted or sponsored by the applicant * * *." The comment explained that a 505(b)(2) applicant could assemble literature demonstrating the safety and effectiveness of a drug product marketed before 1962 (when the Federal Food, Drug, and Cosmetic Act was amended to require new drugs to be safe and effective for their intended uses) or 1938 (when the Food and Drugs Act was amended to require new drugs to be safe for the conditions of their intended use) and, under the rule, seek 5 years of new drug exclusivity. The comment said granting exclusivity to such drugs would be inconsistent with statutory intent and the legislative history.

Under the statute, a drug product may qualify for 5 years of exclusivity if its active moiety has not been previously approved in any other application (see section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act). For some drug products marketed before 1938 or 1962, the active moiety will have been the subject of an approved application (under prior versions of the act or as part of a combination product approved under the act), so the active moiety will be ineligible for 5-year exclusivity.

FDA also notes that the statute provides 5-year exclusivity for applications approved under section 505(b) of the act and that such applications are submitted by persons who wish to introduce or deliver for introduction into interstate commerce "any new drug." (See section 505(a) and (c)(3)(D)(ii).) The term "new drug" is defined in section 201(p) of the act (21 U.S.C. 321(p)). Drug products with active ingredients marketed before 1938 or 1962 may be "new drugs," especially where there has been a change in the product's labeling, composition, or manufacturer.

Products falling within the definition of a "new drug" must be approved under section 505(b) of the act and, as a result, may qualify for 5-year exclusivity under the language of the act and consistent with legislative history.

105. One comment said that FDA should provide 5 years of exclusivity for a single enantiomer of a previously approved racemate. The comment asserted that FDA approval of a racemic drug mixture covers the mixture rather than the enantiomers that compose the mixture.

The agency declines to revise the rule as requested by the comment. As stated in the preamble to the proposed rule, the agency's position is that "a single enantiomer of a previously approved racemate contains a previously approved active moiety and is therefore not considered a new chemical entity" (see 54 FR 28872 at 28898).

106. One comment asked FDA to interpret the phrase "conditions of approval" in proposed § 314.108(b)(4)(iv) narrowly to limit exclusivity to studies conducted by the original applicant. Proposed § 314.108(b)(4) stated that if an application: (i) Was submitted under section 505(b) of the act; (ii) was approved after September 24, 1984; (iii) was for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act; and (iv) contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, the agency will not make effective for a period of 3 years after the date of approval of the

application the approval of a 505(b)(2) application, or an ANDA for the conditions of approval of the original application, or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original NDA. The comment said subsequent applicants who conduct their own studies to obtain approval should not be subject to the original applicant's exclusivity.

FDA believes that the comment misinterprets the scope of exclusivity. As stated in the preamble to the proposed rule and the preamble to this final rule, market exclusivity does not provide any protection from the marketing of a generic version of the same drug product if the generic version is the subject of a full NDA submitted under section 505(b)(1) of the act (see 54 FR 28872 at 28896). As discussed earlier, the statute does not require that the original applicant "conduct" the study to obtain exclusivity. FDA interprets the act to allow for exclusivity where the applicant has supported the study by providing more than 50 percent of the funding or by purchasing exclusive rights to the study.

IV. Analysis of Impacts

FDA has examined the impacts of this rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact on small entities. Title I of Pub. L. 98–417 eliminated unnecessary regulatory barriers for generic drug products and has resulted in generic competition on many important post-1962 drugs. Generic drug sales account for a significant portion of total prescription drug sales, and many of these sales would not have occurred in the absence of Pub. L. 98–417. This competition has saved consumers hundreds of millions of dollars per year, and FDA concludes that this impact is directly attributable to the statute. This rule will not affect the pace or magnitude of this economic impact. The rule simply clarifies and facilitates implementation of the act. Thus, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1980

This final rule contains information collections which have been submitted for approval to the Office of Management and Budget under the Paperwork Reduction Act of 1980. The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions.

Description: The information requirements collect information from persons who must obtain FDA approval before marketing new human drug products or generic versions of previously approved drug products. These persons must submit information to FDA in the form of applications, notices, and certifications. FDA will use this information to determine whether patent information for a drug product has been submitted and whether an applicant is seeking market exclusivity for a particular drug product.

Description of Respondents: Businesses.

ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN

Section	No. of respondents	No. of responses per respondent	Total annual responses	Hours per response	Total hours
314.50(i)	8	1	8	2	16
314.50(j)	50	1	50	2	100
314.52	30	1	30	8	240
314.53	200	1	200	1	200
314.94(a)(12)	215	1	215	2	430
314.95	30	1	30	16	480
314.107	10	1	10	10	10
Total					1,476

There were no comments received on the Paperwork Reduction Act clearance submission or on the burden estimates. The agency has, however, revised the estimate for ANDA's under § 314.94 based on its latest figures for the number of ANDA's received.

VII. References

The following references have been placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Letter dated September 28, 1992, from Jane E. Henney, Deputy Commissioner for Operations, to Alan H. Kaplan and Richard S. Morey, Kleinfeld, Kaplan and Becker (FDA Docket No. 90P–0455).

2. Letter dated December 8, 1987, from John M. Taylor, Associate Commissioner for Regulatory Affairs, to Bruce J. Brennan, Senior Vice President and General Counsel (FDA Docket No. 86P–0235/CP).

List of Subjects in 21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 314 is amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

2. Section 314.50 is amended by redesignating existing paragraph (h) as paragraph (k) and by adding new paragraphs (h), (i), and (j) to read as follows:

§314.50 Content and format of an application.

* * * * *

(h) *Patent information.* The application is required to contain the patent information described under § 314.53.

(i) *Patent certification*—(1) *Contents.* A 505(b)(2) application is required to contain the following:

(i) *Patents claiming drug, drug product, or method of use.* (A) Except as provided in paragraph (i)(2) of this section, a certification with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a drug (the drug product or drug substance that is a component of the drug product) on which investigations that are relied upon by the applicant for approval of its application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505 (b) and (c) of the act and § 314.53. For each such patent, the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(*1*) That the patent information has not been submitted to FDA. The applicant shall entitle such a certification "Paragraph I Certification";

(*2*) That the patent has expired. The applicant shall entitle such a certification "Paragraph II Certification";

(*3*) The date on which the patent will expire. The applicant shall entitle such a certification "Paragraph III Certification"; or

(*4*) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. The applicant shall entitle such a certification "Paragraph IV Certification". This certification shall be submitted in the following form:

I, (*name of applicant*), certify that Patent No. _____ (*is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of*) (*name of proposed drug product*) for which this application is submitted.

The certification shall be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(c) with respect to the content of the notice.

(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the act, the appropriate patent certification under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(ii) *No relevant patents.* If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (*name of applicant*), there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

(iii) *Method of use patent.* (A) If information that is submitted under section 505 (b) or (c) of the act and § 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted under section 505 (b) or (c) of the act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, the applicant shall submit an applicable certification under paragraph (i)(1)(i) of this section.

(2) *Method of manufacturing patent.* An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the drug product for which the applicant is seeking approval.

(3) *Licensing agreements.* If a 505(b)(2) application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant shall submit a certification under paragraph (i)(1)(i)(A)(*4*) of this section ("Paragraph IV Certification") as to that patent and a statement that it has been granted a patent license. If the patent owner consents to an immediate effective date upon approval of the 505(b)(2) application, the application shall contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to an immediate effective date.

(4) *Late submission of patent information.* If a patent described in paragraph (i)(1)(i)(A) of this section is issued and the holder of the approved application for the patented drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification is not required to submit an amended certification. An applicant whose 505(b)(2) application is filed after a late submission of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification at the time of the patent submission shall submit a certification under paragraph (i)(1)(i) or (i)(1)(ii) of this section or a statement under paragraph (i)(1)(iii) of this section as to that patent.

(5) *Disputed patent information.* If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn or changed, the applicant must submit an appropriate certification for each relevant patent.

(6) *Amended certifications.* A certification submitted under paragraphs (i)(1)(i) through (i)(1)(iii) of this section may be amended at any time before the effective date of the approval of the application. An applicant shall submit an amended certification as an amendment to a

pending application or by letter to an approved application. If an applicant with a pending application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. Once an amendment or letter for the change in certification has been submitted, the application will no longer be considered to be one containing the prior certification.

(i) *After finding of infringement.* An applicant who has submitted a certification under paragraph (i)(1)(i)(A)(*4*) of this section and is sued for patent infringement within 45 days of the receipt of notice sent under § 314.52 shall amend the certification if a final judgment in the action is entered finding the patent to be infringed unless the final judgment also finds the patent to be invalid. In the amended certification, the applicant shall certify under paragraph (i)(1)(i)(A)(*3*) of this section that the patent will expire on a specific date.

(ii) *After removal of a patent from the list.* If a patent is removed from the list, any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under paragraph (i)(1)(ii) of this section that no patents described in paragraph (i)(1)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. In the amendment, the applicant shall state the reason for the change in certification (that the patent is or has been removed from the list). A patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. An applicant shall submit an amended certification as an amendment to a pending application. Once an amendment for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (i)(1)(i)(A)(*4*) of this section.

(iii) *Other amendments.* (A) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) of this section, an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate.

(B) An applicant is not required to amend a submitted certification when information on an otherwise applicable patent is submitted after the effective date of approval for the 505(b)(2) application.

(j) *Claimed exclusivity.* A new drug product, upon approval, may be entitled to a period of marketing exclusivity under the provisions of § 314.108. If an applicant believes its drug product is entitled to a period of exclusivity, it shall submit with the new drug application prior to approval the following information:

(1) A statement that the applicant is claiming exclusivity.

(2) A reference to the appropriate paragraph under § 314.108 that supports its claim.

(3) If the applicant claims exclusivity under § 314.108(b)(2), information to show that, to the best of its knowledge or belief, a drug has not previously been approved under section 505(b) of the act containing any active moiety in the drug for which the applicant is seeking approval.

(4) If the applicant claims exclusivity under § 314.108(b)(4) or (b)(5), the following information to show that the application contains "new clinical investigations" that are "essential to approval of the application or supplement" and were "conducted or sponsored by the applicant:"

(i) *"New clinical investigations."* A certification that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in § 314.108(a).

(ii) *"Essential to approval."* A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval, a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the application, and an explanation as to why the studies or reports are insufficient.

(iii) *"Conducted or sponsored by."* If the applicant was the sponsor named in the Form FDA–1571 for an investigational new drug application (IND) under which the new clinical investigation(s) that is essential to the approval of its application was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its application, and information supporting the certification. To demonstrate "substantial support," an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation of why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

* * * * *

3. New sections 314.52 and 314.53 are added to subpart B to read as follows:

§ 314.52 Notice of certification of invalidity or noninfringement of a patent.

(a) *Notice of certification.* For each patent which claims the drug or drugs on which investigations that are relied upon by the applicant for approval of its application were conducted or which claims a use for such drug or drugs and which the applicant certifies under § 314.50(i)(1)(i)(A)(*4*) that a patent is invalid, unenforceable, or will not be infringed, the applicant shall send notice of such certification by registered or certified mail, return receipt requested to each of the following persons:

(1) Each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the United States Patent and Trademark Office; and

(2) The holder of the approved application under section 505(b) of the act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval, or, if

the application holder does not reside or maintain a place of business within the United States, the application holder's attorney, agent, or other authorized official. The name and address of the application holder or its attorney, agent, or authorized official may be obtained from the Division of Drug Information Resources (HFD–80), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(3) This paragraph does not apply to a use patent that claims no uses for which the applicant is seeking approval.

(b) *Sending the notice.* The applicant shall send the notice required by paragraph (a) of this section when it receives from FDA an acknowledgment letter stating that its application has been filed. At the same time, the applicant shall amend its application to include a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirement under paragraph (c) of this section.

(c) *Content of a notice.* In the notice, the applicant shall cite section 505(b)(3)(B) of the act and shall include, but not be limited to, the following information:

(1) A statement that a 505(b)(2) application submitted by the applicant has been filed by FDA.

(2) The application number.

(3) The established name, if any, as defined in section 502(e)(3) of the act, of the proposed drug product.

(4) The active ingredient, strength, and dosage form of the proposed drug product.

(5) The patent number and expiration date, as submitted to the agency or as known to the applicant, of each patent alleged to be invalid, unenforceable, or not infringed.

(6) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant shall include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(7) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) *Amendment to an application.* If an application is amended to include the certification described in § 314.50(i), the applicant shall send the notice required by paragraph (a) of this section at the same time that the amendment to the application is submitted to FDA.

(e) *Documentation of receipt of notice.* The applicant shall amend its application to document receipt of the notice required under paragraph (a) of this section by each person provided the notice. The applicant shall include a copy of the return receipt or other similar evidence of the date the notification was received. FDA will accept as adequate documentation of the date of receipt a return receipt or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the agency.

(f) *Approval.* If the requirements of this section are met, the agency will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved application holder as the first day of the 45-day period provided for in section 505(c)(3)(C) of the act. FDA may, if the applicant amends its application with a written statement that a later date should be used, count from such later date.

§ 314.53 Submission of patent information.

(a) *Who must submit patent information.* This section applies to any applicant who submits to FDA a new drug application or an amendment to it under section 505(b) of the act and § 314.50 or a supplement to an approved application under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) *Patents for which information must be submitted.* An applicant described in paragraph (a) of this section shall submit information on each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents. Process patents are not covered by this section and information on process patents may not be submitted to FDA. For patents that claim a drug substance or drug product, the applicant shall submit information only on those patents that claim a drug product that is the subject of a pending or approved application, or that claim a drug substance that is a component of such a product. For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use of a pending or approved application.

(c) *Reporting requirements*—(1) *General requirements.* An applicant described in paragraph (a) of this section shall submit the following information for each patent described in paragraph (b) of this section:

(i) Patent number and the date on which the patent will expire.

(ii) Type of patent, i.e., drug, drug product, or method of use.

(iii) Name of the patent owner.

(iv) If the patent owner or applicant does not reside or have a place of business within the United States, the name of an agent (representative) of the patent owner or applicant who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and §§ 314.52 and 314.95.

(2) *Formulation, composition, or method of use patents*—(i) *Original declaration.* For each formulation, composition, or method of use patent, in addition to the patent information described in paragraph (c)(1) of this section the applicant shall submit the following declaration:

The undersigned declares that Patent No. _____ covers the formulation, composition, and/or method of use of (*name of drug product*). This product is (*currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act*) [or] (*the subject of this application for which approval is being sought*):

(ii) *Amendment of patent information upon approval.* Within 30 days after the date of approval of its application, if the application contained a declaration required under paragraph (c)(2)(i) of this section, the applicant shall by letter amend the declaration to identify each patent that claims the formulation, composition, or the specific indications or other conditions of use that have been approved.

(3) *No relevant patents.* If the applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with

respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, it shall so declare.

(4) *Authorized signature.* The declarations required by this section shall be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) *When and where to submit patent information*—(1) *Original application.* An applicant shall submit with its original application submitted under this part, including an application described in section 505(b)(2) of the act, the information described in paragraph (c) of this section on each drug (ingredient), drug product (formulation and composition), and method of use patent issued before the application is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the application under § 314.60.

(2) *Supplements.* (i) An applicant shall submit patent information required under paragraph (c) of this section for a patent that claims the drug, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To change the formulation;

(B) To add a new indication or other condition of use, including a change in route of administration;

(C) To change the strength;

(D) To make any other patented change regarding the drug, drug product, or any method of use.

(ii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and existing patents for which information has already been submitted to FDA claim the changed product, the applicant shall submit a certification with the supplement identifying the patents that claim the changed product.

(iii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and no patents, including previously submitted patents, claim the changed product, it shall so certify.

(iv) The applicant shall comply with the requirements for amendment of formulation or composition and method of use patent information under paragraphs (c)(2)(ii) and (d)(3) of this section.

(3) *Patent information deadline.* If a patent is issued for a drug, drug product, or method of use after an application is approved, the applicant shall submit to FDA the required patent information within 30 days of the date of issuance of the patent.

(4) *Copies.* The applicant shall submit two copies of each submission of patent information, an archival copy and a copy for the chemistry, manufacturing, and controls section of the review copy, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, Park Bldg., rm. 2–14, 12420 Parklawn Dr., Rockville, MD 20857. The applicant shall submit the patent information by letter separate from, but at the same time as, submission of the supplement.

(5) *Submission date.* Patent information shall be considered to be submitted to FDA as of the date the information is received by the Central Document Room.

(6) *Identification.* Each submission of patent information, except information submitted with an original application, and its mailing cover shall bear prominent identification as to its contents, i.e., "Patent Information," or, if submitted after approval of an application, "Time Sensitive Patent Information."

(e) *Public disclosure of patent information.* FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each use patent, the approved indications or other conditions of use covered by a patent. FDA will publish such patent information upon approval of the application, or, if the patent information is submitted by the applicant after approval of an application as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the agency of the patent information. Patent information submitted by the last working day of a month will be published in that month's supplement to the list. Patent information received by the agency between monthly publication of supplements to the list will be placed on public display in FDA's Freedom of Information Staff. A request for copies of the file shall be sent in writing to the Freedom of Information Staff (HFI–35), Food and Drug Administration, rm. 12A–16, 5600 Fishers Lane, Rockville, MD 20857.

(f) *Correction of patent information errors.* If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement. Such notification should be directed to the Drug Information Services Branch (HFD–84), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, a 505(b)(2) application or an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

4. Section 314.54 is amended by adding new paragraph (a)(1)(vii) to read as follows:

§ 314.54 Procedure for submission of an application requiring investigations for approval of a new indication for, or other change from, a listed drug.

(a) * * *

(1) * * *

(vii) If the applicant believes the change for which it is seeking approval is entitled to a period of exclusivity, the information required under § 314.50(j).

* * * * *

5. Section 314.70 is amended by adding new paragraph (f) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(f) *Claimed exclusivity.* If an applicant claims exclusivity under § 314.108 upon approval of a supplemental application for a change to its previously approved drug product, the applicant shall include with its supplemental application the information required under § 314.50(j).

6. Section 314.94 is amended by adding a new paragraph (a)(12) to read as follows:

§ 314.94 Content and format of an abbreviated application.

(a) * * *

(12) *Patent certification*—(i) *Patents claiming drug, drug product, or method of use.* (A) Except as provided in paragraph (a)(12)(iv) of this section, a certification with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the act and for which information is required to be filed under section 505(b) and (c) of the act and § 314.53. For each such patent, the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(*1*) That the patent information has not been submitted to FDA. The applicant shall entitle such a certification "Paragraph I Certification";

(*2*) That the patent has expired. The applicant shall entitle such a certification "Paragraph II Certification";

(*3*) The date on which the patent will expire. The applicant shall entitle such a certification "Paragraph III Certification"; or

(*4*) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the abbreviated application is submitted. The applicant shall entitle such a certification "Paragraph IV Certification". This certification shall be submitted in the following form:

I, (*name of applicant*), certify that Patent No. _____ (*is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of*) (*name of proposed drug product*) for which this application is submitted.

The certification shall be accompanied by a statement that the applicant will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the abbreviated new drug application refers to a listed drug that is itself a licensed generic product of a patented drug first approved under section 505(b) of the act, the appropriate patent certification under paragraph (a)(12)(i) of this section with respect to each patent that claims the first-approved patented drug or that claims a use for such drug.

(ii) *No relevant patents.* If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (a)(12)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (*name of applicant*), there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug.

(iii) *Method of use patent.* (A) If patent information is submitted under section 505(b) or (c) of the act and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted under section 505(b) or (c) of the act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, an applicable certification under paragraph (a)(12)(i) of this section.

(iv) *Method of manufacturing patent.* An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the listed drug.

(v) *Licensing agreements.* If the abbreviated new drug application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, a certification under paragraph (a)(12)(i)(A)(*4*) of this section ("Paragraph IV Certification") as to that patent and a statement that it has been granted a patent license.

(vi) *Late submission of patent information.* If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification. An applicant whose abbreviated new drug application is submitted after a late submission of patent information, or whose pending abbreviated application was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, shall submit a certification under paragraph (a)(12)(i) of this section or a statement under paragraph (a)(12)(iii) of this section as to that patent.

(vii) *Disputed patent information.* If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn or changed, the applicant shall submit an appropriate certification for each relevant patent.

(viii) *Amended certifications.* A certification submitted under paragraphs (a)(12)(i) through (a)(12)(iii) of this section may be amended at any time before the effective date of the approval of the application. However, an applicant who has submitted a paragraph IV patent certification may not change it to a paragraph III certification if a patent infringement suit has been filed against another paragraph IV applicant unless the agency has determined that no applicant is entitled to 180-day exclusivity or the patent expires before the lawsuit is resolved or expires after the suit is resolved but before the end of the 180-day exclusivity period. If an applicant with a pending application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. An applicant shall submit an amended certification by letter or as an amendment to a pending application or by letter to an approved application. Once an amendment or letter is submitted, the application will no longer be considered to contain the prior certification.

(A) *After finding of infringement.* An applicant who has submitted a certification under paragraph (a)(12)(i)(A)(*4*) of this section and is sued for patent infringement within 45 days of the receipt of notice sent under § 314.95 shall amend the certification if a final judgment in the action against the applicant is entered finding the patent to be infringed. In the amended certification, the applicant shall certify under paragraph (a)(12)(i)(A)(*3*) of this section that the patent will expire on a specific date. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(*4*) of this section. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.

(B) *After removal of a patent from the list.* If a patent is removed from the list, any applicant with a pending application (including a tentatively

approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under paragraph (a)(12)(ii) of this section that no patents described in paragraph (a)(12)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. In the amendment, the applicant shall state the reason for the change in certification (that the patent is or has been removed from the list). A patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. An applicant shall submit an amended certification. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(4) of this section.

(C) *Other amendments.* (1) Except as provided in paragraphs (a)(12)(vi) and (a)(12)(viii)(C)(*2*) of this section, an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate.

(*2*) An applicant is not required to amend a submitted certification when information on a patent on the listed drug is submitted after the effective date of approval of the abbreviated application.

* * * * *

7. New section 314.95 is added to subpart C to read as follows:

§ 314.95 Notice of certification of invalidity or noninfringement of a patent.

(a) *Notice of certification.* For each patent that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and that the applicant certifies under § 314.94(a)(12) is invalid, unenforceable, or will not be infringed, the applicant shall send notice of such certification by registered or certified mail, return receipt requested to each of the following persons:

(1) Each owner of the patent which is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the United States Patent and Trademark Office; and

(2) The holder of the approved application under section 505(b) of the act for the listed drug that is claimed by the patent and for which the applicant is seeking approval, or, if the application holder does not reside or maintain a place of business within the United States, the application holder's attorney, agent, or other authorized official. The name and address of the application holder or its attorney, agent, or authorized official may be obtained from the Division of Drug Information Resources (HFD–80), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(3) This paragraph does not apply to a use patent that claims no uses for which the applicant is seeking approval.

(b) *Sending the notice.* The applicant shall send the notice required by paragraph (a) of this section when it receives from FDA an acknowledgment letter stating that its abbreviated new drug application is sufficiently complete to permit a substantive review. At the same time, the applicant shall amend its abbreviated new drug application to include a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirements under paragraph (c) of this section.

(c) *Contents of a notice.* In the notice, the applicant shall cite section 505(j)(2)(B)(ii) of the act and shall include, but not be limited to, the following information:

(1) A statement that FDA has received an abbreviated new drug application submitted by the applicant containing any required bioavailability or bioequivalence data or information.

(2) The abbreviated application number.

(3) The established name, if any, as defined in section 502(e)(3) of the act, of the proposed drug product.

(4) The active ingredient, strength, and dosage form of the proposed drug product.

(5) The patent number and expiration date, as submitted to the agency or as known to the applicant, of each patent alleged to be invalid, unenforceable, or not infringed.

(6) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant shall include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(7) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) *Amendment to an abbreviated application.* If an abbreviated application is amended to include the certification described in § 314.94(a)(12)(i)(A)(4), the applicant shall send the notice required by paragraph (a) of this section at the same time that the amendment to the abbreviated application is submitted to FDA.

(e) *Documentation of receipt of notice.* The applicant shall amend its abbreviated application to document receipt of the notice required under paragraph (a) of this section by each person provided the notice. The applicant shall include a copy of the return receipt or other similar evidence of the date the notification was received. FDA will accept as adequate documentation of the date of receipt a return receipt or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the agency.

(f) *Approval.* If the requirements of this section are met, FDA will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved application holder as the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the act. FDA may, if the applicant provides a written statement to FDA that a later date should be used, count from such later date.

8. Section 314.101 is amended by revising paragraph (e) to read as follows:

§ 314.101 Filing an application and an abbreviated antibiotic application and receiving an abbreviated new drug application.

* * * * *

(e) The agency will refuse to file an application or abbreviated antibiotic application or will consider an abbreviated new drug application not to have been received if any of the following applies:

(1) The drug product is subject to licensing by FDA under the Public

Health Service Act (42 U.S.C. 201 *et seq.*) and subchapter F of this chapter.

(2) In the case of a 505(b)(2) application or an abbreviated new drug application, the drug product contains the same active moiety as a drug that:

(i) Was approved after September 24, 1984, in an application under section 505(b) of the act, and

(ii) Is entitled to a 5-year period of exclusivity under section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act and § 314.108(b)(2), unless the 5-year exclusivity period has elapsed or unless 4 years of the 5-year period have elapsed and the application or abbreviated application contains a certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(A)(*4*) or § 314.94(a)(12)(i)(A)(*4*).

* * * * *

9. New sections 314.107 and 314.108 are added to subpart D to read as follows:

§ 314.107 Effective date of approval of a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act.

(a) *General.* A drug product may be introduced or delivered for introduction into interstate commerce when approval of the application or abbreviated application for the drug product becomes effective. Except as provided in this section, approval of an application or abbreviated application for a drug product becomes effective on the date FDA issues an approval letter under § 314.105 for the application or abbreviated application.

(b) *Effect of patent on the listed drug.* If approval of an abbreviated new drug application submitted under section 505(j) of the act or of a 505(b)(2) application is granted, that approval will become effective in accordance with the following:

(1) *Date of approval letter.* Except as provided in paragraphs (b)(3), (b)(4), and (c) of this section, approval will become effective on the date FDA issues an approval letter under § 314.105 if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that:

(i) There are no relevant patents; or

(ii) The applicant is aware of a relevant patent but the patent information required under section 505 (b) or (c) of the act has not been submitted to FDA; or

(iii) The relevant patent has expired; or

(iv) The relevant patent is invalid, unenforceable, or will not be infringed.

(2) *Patent expiration.* If the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent will expire on a specified date, approval will become effective on the specified date.

(3) *Disposition of patent litigation.* (i)(A) Except as provided in paragraphs (b)(3)(ii), (b)(3)(iii), and (b)(3)(iv) of this section, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt by the patent owner of the notice of certification from the applicant under § 314.52 or § 314.95, approval may be made effective 30 months after the date of the receipt of the notice of certification by the patent owner or by the exclusive licensee (or their representatives) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action; or

(B) If the patented drug product qualifies for 5 years of exclusive marketing under § 314.108(b)(2) and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date the patented drug was approved and within 45 days of receipt by the patent owner of the notice of certification, the approval may be made effective at the expiration of the 7½ years from the date of approval of the application for the patented drug product.

(ii) If before the expiration of the 30-month period, or 7½ years where applicable, the court issues a final order that the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date the court enters judgment;

(iii) If before the expiration of the 30-month period, or 7½ years where applicable, the court issues a final order or judgment that the patent has been infringed, approval may be made effective on the date the court determines that the patent will expire or otherwise orders; or

(iv) If before the expiration of the 30-month period, or 7½ years where applicable, the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date the court enters a final order or judgment that the patent is invalid, unenforceable, or not infringed.

(v) In order for an approval to be made effective under paragraph (b)(3) of this section, the applicant must receive an approval letter from the agency indicating that the application has received final approval. Tentative approval of an application does not constitute "approval" of an application and cannot, absent a final approval letter from the agency, result in an effective approval under paragraph (b)(3) of this section.

(4) *Multiple certifications.* If the applicant has submitted certifications under § 314.50(i) or § 314.94(a)(12) for more than one patent, the date of approval will be calculated for each certification, and the approval will become effective on the last applicable date.

(c) *Subsequent abbreviated new drug application submission.*

(1) If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the same patent was invalid, unenforceable, or would not be infringed and the applicant submitting the first application has successfully defended against a suit for patent infringement brought within 45 days of the patent owner's receipt of notice submitted under § 314.95, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:

(i) The date the applicant submitting the first application first commences commercial marketing of its drug product; or

(ii) The date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed.

(2) For purposes of paragraph (c)(1) of this section, the "applicant submitting the first application" is the applicant that submits an application that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification. A "substantially complete" application must contain the results of any required bioequivalence studies, or, if applicable, a request for a waiver of such studies.

(3) For purposes of paragraph (c)(1) of this section, if FDA concludes that the

applicant submitting the first application is not actively pursuing approval of its abbreviated application, FDA will make the approval of subsequent abbreviated applications immediately effective if they are otherwise eligible for an immediately effective approval.

(4) For purposes of paragraph (c)(1)(i) of this section, the applicant submitting the first application shall, if sued for patent infringement, notify FDA of the date that it commences commercial marketing of its drug product. Commercial marketing commences with the first date of introduction or delivery for introduction into interstate commerce outside the control of the manufacturer of a drug product, except for investigational use under part 312 of this chapter, but does not include transfer of the drug product for reasons other than sale within the control of the manufacturer or application holder. If an applicant does not promptly notify FDA of such date, the effective date of approval shall be deemed to be the date of the commencement of first commercial marketing.

(d) *Delay due to exclusivity.* The agency will also delay the effective date of the approval of an abbreviated new drug application under section 505(j) of the act or a 505(b)(2) application if delay is required by the exclusivity provisions in § 314.108. When the effective date of an application is delayed under both this section and § 314.108, the effective date will be the later of the 2 days specified under this section and § 314.108.

(e) *Court actions.* (1) References to actions of "the court" in paragraphs (b) and (c) of this section are to the court that enters final judgment from which no appeal can be or has been taken.

(2) For purposes of establishing the effective date of approval based on a court judgment, the following dates shall be deemed to be the date of the final decision of the court on the patent issues:

(i) If the district court enters a decision that the patent is invalid, unenforceable, or not infringed, and the decision is not appealed, the date on which the right to appeal lapses.

(ii) If the district court enters a decision that the patent is invalid, unenforceable, or not infringed, and the decision is appealed, the date of the first decision or order by a higher court holding or affirming the decision of the district court that the patent is invalid, unenforceable, or not infringed.

(iii) If the district court enters a decision that the patent is infringed, and the decision is appealed, the date on which the district court enters a judgment that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by a court of appeals.

(iv) The applicant shall submit a copy of the entry of the order or judgment to the Office of Generic Drugs (HFD–600), or to the appropriate division in the Office of Drug Evaluation I (HFD–100) or Office of Drug Evaluation II (HFD–500), whichever is applicable, within 10 working days of a final judgment.

(f) *Computation of 45-day time clock.* (1) The 45-day clock described in paragraph (b)(3) of this section begins on the day after the date of receipt of the applicant's notice of certification by the patent owner or its representative, and by the approved application holder. When the 45th day falls on Saturday, Sunday, or a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(2) The abbreviated new drug applicant or the 505(b)(2) applicant shall notify FDA immediately of the filing of any legal action filed within 45 days of receipt of the notice of certification. If the applicant submitting the abbreviated new drug application or the 505(b)(2) application or patent owner or its representative does not notify FDA in writing before the expiration of the 45-day time period or the completion of the agency's review of the application, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of certification, approval of the abbreviated new drug application or the 505(b)(2) application will be made effective immediately upon expiration of the 45 days or upon completion of the agency's review and approval of the application, whichever is later. The notification to FDA of the legal action shall include:

(i) The abbreviated new drug application or 505(b)(2) application number.

(ii) The name of the abbreviated new drug or 505(b)(2) application applicant.

(iii) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.

(iv) A certification that an action for patent infringement identified by number, has been filed in an appropriate court on a specified date.

The applicant of an abbreviated new drug application shall send the notification to FDA's Office of Generic Drugs (HFD–600). A 505(b)(2) applicant shall send the notification to the appropriate division in the Center for Drug Evaluation and Research reviewing the application. A patent owner or its representative may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in this paragraph.

(3) If the patent owner or approved application holder who is an exclusive patent licensee waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or approved application holder who is an exclusive patent licensee submits to FDA a valid waiver before the 45 days elapse, approval of the abbreviated new drug application or the 505(b)(2) application will be made effective upon completion of the agency's review and approval of the application. FDA will only accept a waiver in the following form:

(*Name of patent owner or exclusive patent licensee*) has received notice from (*name of applicant*) under (*section 505(b)(3) or 505(j)(2)(B) of the act*) and does not intend to file an action for patent infringement against (*name of applicant*) concerning the drug (*name of drug*) before (*date on which 45 days elapses.* (*Name of patent owner or exclusive patent licensee*) waives the opportunity provided by (*section 505(c)(3)(C) or 505(j)(B)(iii) of the act*) and does not object to FDA's approval of (*name of applicant*)'s (*505(b)(2) or abbreviated new drug application*) for (*name of drug*) with an immediate effective date on or after the date of this letter.

§ 314.108 New drug product exclusivity.

(a) *Definitions.* The following definitions of terms apply to this section:

Active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Approved under section 505(b) means an application submitted under section 505(b) and approved on or after October 10, 1962, or an application that was "deemed approved" under section 107(c)(2) of Pub. L. 87–781.

Clinical investigation means any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

Conducted or sponsored by the applicant with regard to an investigation means that before or during the investigation, the applicant was named in Form FDA–1571 filed with FDA as the sponsor of the

investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation. To demonstrate "substantial support," an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

Date of approval means the date on the letter from FDA stating that the new drug application is approved, whether or not final printed labeling or other materials must yet be submitted as long as approval of such labeling or materials is not expressly required. "Date of approval" refers only to a final approval and not to a tentative approval that may become effective at a later date.

Essential to approval means, with regard to an investigation, that there are no other data available that could support approval of the application.

FDA means the Food and Drug Administration.

New chemical entity means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.

New clinical investigation means an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.

(b) *Submission of and effective date of approval of an abbreviated new drug application submitted under section 505(j) of the act or a 505(b)(2) application.* (1) [Reserved]

(2) If a drug product that contains a new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application, except that the 505(b)(2) application or abbreviated application may be submitted after 4 years if it contains a certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(A)(*4*) or § 314.94(a)(12)(i)(A)(*4*).

(3) The approval of a 505(b)(2) application or abbreviated application described in paragraph (b)(2) of this section will become effective as provided in § 314.107(b)(1) or (b)(2), unless the owner of a patent that claims the drug, the patent owner's representative, or exclusive licensee brings suit for patent infringement against the applicant during the 1-year period beginning 48 months after the date of approval of the new drug application for the new chemical entity and within 45 days after receipt of the notice described at § 314.52 or § 314.95, in which case, approval of the 505(b)(2) application or abbreviated application will be made effective as provided in § 314.107(b)(3).

(4) If an application:

(i) Was submitted under section 505(b) of the act;

(ii) Was approved after September 24, 1984;

(iii) Was for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act; and

(iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, the agency will not make effective for a period of 3 years after the date of approval of the application the approval of a 505(b)(2) application or an abbreviated new drug application for the conditions of approval of the original application, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original new drug application.

(5) If a supplemental application:

(i) Was approved after September 24, 1984; and

(ii) Contained reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant that were essential to approval of the supplemental application, the agency will not make effective for a period of 3 years after the date of approval of the supplemental application the approval of a 505(b)(2) application or an abbreviated new drug application for a change, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting a change approved in the supplemental new drug application.

Dated: September 23, 1994.

William K. Hubbard,

Interim Deputy Commissioner for Policy.

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